PRIOR AUTHORIZATION POLICY

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

REVIEW DATE: 04/26/2023; selected revision 01/17/2024

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CIGNA NATIONAL FORMULARY COVERAGE:

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 statin therapy for the treatment primary hyperlipidemia in adults with the following:[1]

- **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 safety and effectiveness have not been established in pediatric patients.[1]

Guidelines

Many guidelines are available regarding the treatment of patients with dyslipidemia which include the management of HeFH and ASCVD.[2-7] 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 College of Cardiology Expert Consensus Decision Pathway on the Role of Non-Statin Therapies** for LDL-Cholesterol Lowering in the Management of ASCVD Risk (2022) make several recommendations; Nexletol® (bempedoic acid tablets) is addressed.[2] For adults with clinical ASCVD at very high risk (e.g., patients with major ASCVD events, HeFH, diabetes) who are on statin therapy for secondary prevention, the general goal is ≥ 50% LDL-C reduction and an LDL-C < 55 mg/dL (of non-HDL-C < 85 mg/dL) with maximally tolerated statin therapy. If the above goals are not achieved, the initial non-statin agents recommended include ezetimibe and/or a proprotein convertase subtilisin kexin type 9 monoclonal antibody (i.e., Repatha or Praluent). Nexletol can be considered after these therapies.
- The **American Association of Clinical Endocrinologists and American College of Endocrinology** has guidelines regarding the management of dyslipidemia and the prevention of CV disease (2020).[7] Nexletol is mentioned is cited as an option for intensification of therapy after use of standard agents such as high-intensity/moderate-intensity statins.
- The **American Heart Association (AHA)/American College of Cardiology** guidelines on the management of blood cholesterol (2018) define ACSVD as acute coronary syndrome (ACS), those with a history of myocardial infarction, stable or unstable angina or coronary or other revascularizations, stroke, transient ischemic attack, or peripheral arterial disease.[3,4] 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).[8] 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. A patient who has previously met Initial Therapy criteria for Nexlizet for the requested indication under the Coverage Review Department and is currently receiving Nexlizet is only required to meet continuation of therapy criteria (i.e., currently receiving therapy). If past criteria has not been met under the Coverage Review Department and the patient is currently receiving Nexlizet, or is restarting Nexlizet, Initial Therapy criteria must be met.

- **Nexlizet® (bempedoic acid and ezetimibe tablets (Esperion)**

is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indications

1. **Atherosclerotic Cardiovascular Disease.** Approve for 1 year if the patient meets all of the following (A or B):
   - **A)** Initial Therapy. Approve if the patient meets all of the following (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has had one of the following conditions or diagnoses (a, b, c, d, e, or f):
       - **a)** A previous myocardial infarction or a history of an acute coronary syndrome; OR
       - **b)** Angina (stable or unstable); OR
       - **c)** A past history of stroke or transient ischemic attack; OR
       - **d)** Coronary artery disease; OR
       - **e)** Peripheral arterial disease; OR
       - **f)** 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.
     - **iii.** Patient meets one of the following criteria (a or b):
       - **a)** Patient meets both of the following [(1) and (2)]:
         - **(1)** 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
         - **(2)** Low-density lipoprotein cholesterol level after therapy regimen remains ≥ 70 mg/dL; OR
       - **b)** Patient has been determined to be statin intolerant by meeting one of the following criteria [(1) or (2)]:
         - **(1)** 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
         - **(2)** Patient meets all of the following [(a), (b), and (c)]:
           - **(a)** 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).
           - **(b)** The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND
           - **(c)** 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); OR

Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

B) Patient Currently Receiving Nexlizet. Approve if according to the prescriber, the patient has experienced a response to therapy.

Note: Examples of a response to therapy include decreasing low-density lipoprotein cholesterol (LDL-C), total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Nexlizet for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Nexlizet, Initial Therapy criteria must be met.

2. Heterozygous Familial Hypercholesterolemia (HeFH). Approve for 1 year if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets all of the following (i, ii, or iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient meets one of the following criteria (a, b, or c):

a) Patient has an untreated low-density lipoprotein cholesterol (LDL-C) level ≥ 190 mg/dL (prior to treatment with antihyperlipidemic agents); OR

b) Patient has genetic confirmation of heterozygous familial hypercholesterolemia 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

c) Patient has been diagnosed with heterozygous familial hypercholesterolemia by meeting one of the following diagnostic criteria thresholds [(1) or (2)]:

(1) Prescriber confirms that the Dutch Lipid Network criteria score was > 5; OR

(2) Prescriber confirms that Simone Broome criteria met the threshold for "definite" or "possible (or probable)" familial hypercholesterolemia; AND

iii. Patient meets one of the following (a or b):

a) Patient meets both of the following [(1) and (2)]:

(1) 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

(2) LDL-C level after this treatment regimen remains ≥ 70 mg/dL; OR

b) Patient has been determined to be statin intolerant by meeting one of the following [(1) or (2)]:

(1) 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

(2) Patient meets all of the following [(a), (b), and (c)]:

(a) 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).

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

(c) 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); OR

Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

B) Patient Currently Receiving Nexlizet. Approve if according to the prescriber, the patient has experienced a response to therapy.

Note: Examples of a response to therapy include decreasing low-density lipoprotein cholesterol (LDL-C), total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Nexlizet for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Nexlizet, Initial Therapy criteria must be met.

CONDITIONS NOT COVERED

- **Nexlizet® (bempedoic acid and ezetimibe tablets (Esperion) is(are) considered experimental, investigational or unproven for ANY other use(s).**

REFERENCES

1. Nexletol® tablets [prescribing information]. Ann Arbor, MI: Esperion; December 2023.
2. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. *J Am Coll Cardiol*. 2022;80(14):1366-1418.
3. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. *J Am Coll Cardiol*. 2014;63(25 Pt B):2889-2934.
4. Grundy SM, Stone NJ, Bailey AL, et al. 2018 ACC/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139(35):e1082-1143.

5. Newman CB, Blaha MJ, Boord JB, et al. Lipid management in patients with endocrine disorders: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2020;105(12):3613-3682.
6. 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.
7. Handelsman Y, Jellinger PS, Guerin CK, et al. Consensus Statement by the American Association of Clinical Endocrinologists and the American College of Endocrinology on the management of dyslipidemia and prevention of cardiovascular disease algorithm-2020 executive summary. *Endocr Pract*. 2020;26(10):1196-1124.
8. Gidding SS, Champagne MA, de Ferranti SD, et al. The agenda for familial hypercholesterolemia. A scientific statement from the American Heart Association. *Circulation*. 2015;132(22):2167-2192.
9. Haase A, Goldberg AC. Identification of people with heterozygous familial hypercholesterolemia. *Curr Opin Lipidol*. 2012;23:282-289.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/13/2022
Annual Revision	It was added to the Policy Statement that a patient who has previously met initial therapy criteria for Nexlizet for the requested indication under the Coverage Review Department and is currently receiving Nexlizet is only required to meet continuation of therapy criteria (i.e., currently receiving therapy). If past criteria has not been met under the Coverage Review Department and the patient is currently receiving Nexlizet, or is restarting Nexlizet, initial criteria must be met. **Atherosclerotic Cardiovascular Disease:** Requirements were divided to distinguish between initial therapy and patient currently receiving Nexlizet (previously there was only one criteria set). For a patient who is currently receiving Nexlizet and has previously met initial therapy criteria for the requested indication under the Coverage Review Department, only the continuation of therapy criteria has to be met, which was newly developed. The continuation of therapy criteria states that according to the prescriber, the patient has experienced a response to therapy with examples provided in a Note. **Heterozygous Familial Hypercholesterolemia:** Requirements were divided to distinguish between initial therapy and patient currently receiving Nexlizet (previously there was only one criteria set). The criteria to confirm the diagnosis of heterozygous familial hypercholesterolemia were reworded regarding the use of the Dutch Lipid Network criteria and the Simon Broome criteria; also, the phrase "prescriber used" was changed to "the prescriber confirms". For a patient who is currently receiving Nexlizet and has previously met initial therapy criteria for the requested indication under the Coverage Review Department, only the continuation of therapy criteria has to be met, which was newly developed. The continuation of therapy criteria states that according to the prescriber, the patient has experienced a response to therapy with examples provided in a Note.	04/26/2023
Update	01/03/2024: No criteria changes. Updated the wording of the indication.	NA
Selected Revision	**Atherosclerotic Cardiovascular Disease:** Coronary artery disease was added as a condition or diagnosis that represents this indication of use in this related requirement.	01/17/2024

APPENDIX A

Simon Broome Register Diagnostic Criteria.[9]

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.[8]

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.