PRIOR AUTHORIZATION POLICY

POLICY: Hyperlipidemia – Nexletol Prior Authorization Policy
- Nexletol® (bempedoic acid tablets – Esperion)

REVIEW DATE: 04/26/2023; selected revision 05/03/2023 and 01/17/2024

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CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Nexletol, an adenosine triphosphate-citrate lyase inhibitor, is indicated as an adjunct to diet and statin therapy for the treatment of 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]

Clinical Efficacy

CLEAR Outcomes was a randomized, double-blind, placebo-controlled trial involving 13,970 adults, 18 to 85 years of age who were unable or unwilling to take statins due to unacceptable adverse events among those who had, or were at high risk for, CV disease.[2] Those eligible had to report being statin intolerant. Patients were assigned to receive Nexletol or placebo. Use of statins at very low doses were permitted, as well as other lipid lowering therapies (e.g., ezetimibe, bile acid sequestrants, fibrates). The mean patient age was 65 years. In total, 70% of patients had a previous CV event (secondary prevention population) whereas 30% of patients

were categorized as being in the primary prevention group. At baseline, 22.7% of patients were utilizing a statin and 11.5% were on ezetimibe. The mean LDL-C at baseline was 139 mg/dL. The median follow-up was 40.6 months. The mean LDL-C level after 6 months of treatment with Nexletol was 107 mg/dL for the Nexletol group vs. 136 mg/dL for placebo. The primary endpoint (death from CV causes, nonfatal myocardial infarction [MI], nonfatal stroke, or coronary revascularization) occurred in 11.7% of patients in the Nexletol group vs. 13.3% in the placebo group (P = 0.004). The composite of death from CV causes, nonfatal stroke, or nonfatal MI occurred in 8.2% of patients given Nexletol vs. 9.5% of patients in the placebo group (P = 0.006).

Guidelines

Many guidelines are available regarding the treatment of patients with dyslipidemia which include the management of HeFH and ASCVD.[3-10] 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 is addressed.[3] 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 (PCSK9) 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 **International Lipid Expert Panel** published a position paper in 2023 on use of Nexletol in the management of lipid disorders and CV risk.[10] One recommendation is that in patients with statin intolerance, Nexletol monotherapy, or in combination with ezetimibe and other non-statin drugs is recommended to enable patients to achieve therapeutic goals. In primary prevention, Nexletol may be considered for patients at high and very high CV risk who despite optimally maximally tolerated doses of statins and ezetimibe, are not achieving target LDL-C levels.
- The **American Heart Association (AHA)/American College of Cardiology** guidelines on the management of blood cholesterol (2018) define ACSVD as acute coronary syndrome, those with a history of MI, stable or unstable angina or coronary or other revascularizations, stroke, transient ischemic attack, or peripheral arterial disease.[4,5] An LDL-C < 70 mg/dL is recommended for most

patients with ASCVD to reduce CV risk. Guidelines and reviews have recognize that patients with an elevated coronary artery calcium or calcification score (e.g., ≥ 300 Agatston units) are at an increased risk of CV events.[8,11-14]

- **The AHA** published a scientific statement regarding familial hypercholesterolemia (2015).[9] 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 Nexletol. All approvals are provided for the duration noted below. A patient who has previously met Initial Therapy criteria for Nexletol for the requested indication under the Coverage Review Department and is currently receiving Nexletol 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 Nexletol, or is restarting Nexletol, Initial Therapy criteria must be met.

- **Nexletol® (bempedoic acid 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 ONE 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 (a or b):

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

(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]); AND

(2) Patient has tried one high-intensity statin above along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND

(3) Low-density lipoprotein cholesterol 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: 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]); 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 Nexletol. 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 Nexletol for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Nexletol, 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, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient meets one of the following (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 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

c) Patient has been diagnosed with heterozygous familial hypercholesterolemia 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 all of the following [(1), (2), and (3)]:

(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]); AND

(2) Patient has tried one high-intensity statin above along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND

(3) 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: 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]); 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 Nexletol. 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 Nexletol for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Nexletol, Initial Therapy criteria must be met.

Other Uses with Supportive Evidence

3. Primary Hyperlipidemia.* Approve for 1 year if the patient meets ONE of the following (A or B):

Note: This is not associated with atherosclerotic cardiovascular disease (ASCVD) or heterozygous familial hypercholesterolemia (HeFH) and may be referred to as combined hyperlipidemia, hypercholesterolemia (pure, primary), dyslipidemia, or increased/elevated low-density lipoprotein cholesterol (LDL-C) levels.

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 a coronary artery calcium or calcification score ≥ 300 Agatston units; AND

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

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

(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]); AND

(2) Patient has tried the one high-intensity statin therapy above along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND

(3) LDL-C level after this treatment regimen remains ≥ 100 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: 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]).

(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 Nexletol. 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 Nexletol for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Nexletol, Initial Therapy criteria must be met.

Note:

* A patient may have diagnoses that pertain to more than one indication, therefore, consider review under different approval conditions, if applicable (e.g., a patient with heterozygous familial hypercholesterolemia may have had a clinical ASCVD event, a patient with primary hyperlipidemia may have heterozygous familial hypercholesterolemia).

CONDITIONS NOT COVERED

- **Nexletol® (bempedoic acid tablets (Esperion)**

is(are) considered experimental, investigational or unproven for ANY other use(s).

REFERENCES

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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 Nexletol for the requested indication under the Coverage Review Department and is currently receiving Nexletol 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 Nexletol, or is restarting Nexletol, initial criteria must be met. In addition, the following changes were made: **Atherosclerotic Cardiovascular Disease:** Requirements were divided to distinguish between initial therapy and patient currently receiving Nexletol (previously there was only one criteria set). For a patient who is currently receiving Nexletol 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	04/26/2023 (criteria changes done with Selected Revision changes on 05/03/2023).

	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 Nexletol (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 Nexletol 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.	
Selected Revision	**Atherosclerotic Cardiovascular Disease:** A Note was added that a patient may have diagnoses that pertain to more than one indication, therefore, consider review under different approval conditions, if applicable. **Heterozygous Familial Hypercholesterolemia:** A Note was added that a patient may have diagnoses that pertain to more than one indication, therefore, consider review under different approval conditions, if applicable. **Primary Hyperlipidemia:** This was a new indication added under Other Uses with Supportive Evidence.	05/03/2023
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.[15]

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 patient < 16 years of age; OR
--Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in a patient > 16 years of age;
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 patient < 16 years of age; OR
--Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in a patient > 16 years of age;
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 patient < 16 years of age; OR
--Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in a patient > 16 years of age;
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.[9]

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
Patient is < 18 years of age 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.