PRIOR AUTHORIZATION POLICY

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

REVIEW DATE: 05/08/2024

OVERVIEW

Nexletol, an adenosine triphosphate-citrate lyase inhibitor, is indicated for the following uses:[1]

- To 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: 1) **established cardiovascular disease** (CVD), or 2) **at high risk for a CVD event but without established CVD**.
- **Primary hyperlipidemia**, including **heterozygous familial hypercholesterolemia** (HeFH), in adults 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.

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. Patients had or were at high risk for CVD.[1,2] Patients without established CVD were considered high risk for CVD based on meeting at least one of the following: diabetes mellitus (type 1 or type 2) in females > 65 years of age or males > 60 years of age; a Reynolds Risk score > 30% or a SCORE Risk score > 7.5% over 10 years; or a coronary artery calcium score > 400 Agatston units at any time in the past.[1] Patients were assigned to receive Nexletol or placebo.[1,2] 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 cardiovascular (CV) event (secondary prevention population) whereas 30% of patients were categorized as being in the primary prevention group. In total, 38% of patients were receiving at least one lipid-modifying therapy. At baseline, 23% of patients were utilizing a statin and 12% of patients 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 vs. 136 mg/dL for placebo. The primary endpoint (death from CV causes, nonfatal MI, nonfatal stroke, or coronary revascularization) occurred in 11.7% of patients in the Nexletol group vs. 13.3% of patients in the placebo group (P = 0.004). The composite endpoint (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.[3-11] 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 (ACC) Expert Consensus Decision Pathway on the Role of Non-Statin Therapies** for LDL-Cholesterol Lowering in the Management of Atherosclerotic

Cardiovascular Disease (ASCVD) Risk (2022) make several recommendations.[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 (or non-high-density lipoprotein cholesterol [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® [evolocumab subcutaneous injection] or Praluent® [alirocumab subcutaneous injection]). Nexletol can be considered after these therapies.

- The **American Heart Association (AHA)/ACC** guidelines on the management of blood cholesterol (2018) define patients with ACSVD as those with 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 recognized that patients with an elevated coronary artery calcium or calcification score (e.g., ≥ 300 Agatston units) are at an increased risk of CV events.[13-16]
- The **American Diabetes Association Standards of Care for Diabetes** discuss CV disease and risk management (2024).[8] For patients with diabetes who are 40 to 75 years of age at higher CV risk (including those with one or more ASCVD risk factors), it is recommended to use high-intensity statin therapy to reduce LDL-C by ≥ 50% of baseline and to target an LDL-C of < 70 mg/dL. Also, for patients with diabetes who are 40 to 75 years of age at higher CV risk, especially those with multiple ASCVD risk factors and an LDL-C ≥ 70 mg/dL, it may be reasonable to add ezetimibe or a PCSK9 inhibitor to a maximum tolerated statin. In patients with diabetes intolerant to statin therapy, treatment with Nexletol is recommended to reduce CV event rates as an alternative cholesterol-lowering plan.
- Guidelines for **Chronic Coronary Disease from the AHA and ACC** (along with other organizations) [2023] state in such patients who are judged to be at very high risk and on maximally tolerated statin therapy and with an LDL-C ≥ 70 mg/dL, ezetimibe can be beneficial to further reduce the risk of a major adverse coronary event.[9] Patients with chronic coronary disease who are considered to be at very high risk who have an LDL-C ≥ 70 mg/dL who are receiving maximally tolerated statins and ezetimibe, a PCSK9 monoclonal antibody can be beneficial to further reduce the risk of a major adverse coronary event. In patients with chronic coronary disease who are on maximally tolerated statin therapy who have an LDL-C ≥ 70 mg/dL and in whom ezetimibe and a PCSK9 monoclonal antibody are not adequate or are not tolerated, it may be reasonable to add Nexletol.
- 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 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 AHA** published a scientific statement regarding familial hypercholesterolemia (2015).[11] 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%.[11] Other information also provides guidance on the diagnosis of HeFH.[12]

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 have 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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

1. **Established 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 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 ≥ 55 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 phenotypic confirmation of heterozygous familial hypercholesterolemia; OR
Note: Examples include pathogenic variants at the low-density lipoprotein receptor (LDLR), apolipoprotein B (apo B), proprotein convertase subtilisin kexin type 9 (PCSK9), or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene.
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 Simon 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) 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.

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

Note: This is not associated with established cardiovascular disease 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 meets ONE of the following (a or b):

a) Patient has a coronary artery calcium or calcification score ≥ 300 Agatston units; OR

b) Patient has diabetes; 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 ≥ 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]).

(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 a diagnosis that pertains to more than one indication, therefore, consider review under different approval conditions, if applicable (e.g., a patient with heterozygous familial hypercholesterolemia may have established cardiovascular disease, a patient with primary hyperlipidemia may have heterozygous familial hypercholesterolemia).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nexletol 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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APPENDIX A

Simon Broome Register Diagnostic Criteria.[11,12]
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.[11,12]

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.