Nexletol (bempedoic acid)
Nexlizet (bempedoic acid/ezetimibe)

NOTICE

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BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the Nexletol (bempedoic acid) and Nexlizet (bempedoic acid and ezetimibe) drug policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines and clinical studies. The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

Nexletol (bempedoic acid) and Nexlizet (bempedoic acid and ezetimibe) are both Food and Drug Administration (FDA) indicated as an adjunct to diet and maximally tolerated statin therapy for both the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) and adults with established atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C).

Limitations of Use

The effect of Nexletol and Nexlizet on cardiovascular morbidity and mortality has not been determined.

POLICY

Required Documentation

The following information is necessary to initiate the prior authorization review:

- Untreated baseline LDL level, LDL levels while receiving statin therapy (prior to starting Nexletol/Nexlizet therapy) and current LDL levels on Nexletol/Nexlizet (if applicable)
- Chart notes demonstrating the patient is engaging in healthy lifestyle changes (low-fat diet and exercise regimen)
- Chart notes demonstrating statin intolerance or contraindication to statin therapy (if applicable)
- Lab results (i.e. LDL-receptor mutation, familial defective apo B-100, or PCSK9 gain-of-function mutation) or rating scale (i.e. Simon-Broome Diagnostic Criteria or Dutch Lipid Network Criteria) demonstrating heterozygous familial hypercholesterolemia diagnosis (if applicable)

Criteria for Initial Approval

A. Nexletol (bempedoic acid) and Nexlizet (bempedoic acid and ezetimibe) may be considered **medically necessary** for the treatment of **clinical atherosclerotic cardiovascular disease (ASCVD)** [Appendix A] when the following criteria is met:

1. Patient is 18 years of age or older
2. Patient is engaging in aggressive lifestyle modifications (Appendix B)
3. Patient has been unable to achieve an LDL-C < 70 mg/dL despite adherence to the combination of lifestyle changes and at least three months of the following lipid lowering therapy:
   a). A trial of BOTH high-intensity statins (atorvastatin 40-80 mg and rosuvastatin 20-40 mg) at a maximum tolerated dose in combination with ezetimibe, **OR**
   b). A trial of TWO moderate intensity statins (e.g. pravastatin 40-80 mg, lovastatin 40 mg, fluvastatin 80 mg, pitavastatin 2-4 mg, simvastatin 20-40 mg) in combination with ezetimibe, only in the event the patient is unable to complete either of the high-intensity statin trials at the maximum approved dosing
4. Nexletol will be added to statin and ezetimibe therapy or Nexlizet will be added to statin therapy

OR

1. Patient is 18 years of age or older
2. Patient is engaging in aggressive lifestyle modifications
3. Patient has a documented contraindication (e.g., active liver disease, pregnancy, breastfeeding), or medically justifiable reason that precludes statin use (e.g. patient has experienced rhabdomyolysis, CK elevations ≥ 10x ULN, or statin intolerance).
   a). Statin intolerance shall be defined in accordance with the National Lipid Association definition:
      i. Inability to tolerate at least two statins (one at any dose, one at lowest daily dose) due to objectionable symptoms or abnormal biomarkers temporally related to statin use, reversible upon statin discontinuation and reproducible by re-challenge while excluding other known determinants. Other known determinants include low body mass index (BMI), acute infection, untreated or undertreated hypothyroidism, severe renal or hepatic dysfunction, organ transplant, recent severe trauma, HIV infection, Vitamin D deficiency, history of creatine kinase elevation, history of preexisting or unexplained muscle or joint pain, high level of physical activity, illicit drug abuse, excess alcohol use. Each statin trial, both initial and re-challenge shall be at least two weeks duration.
         - A trial of one statin at lowest starting daily dose
            - Rosuvastatin 5mg
            - Atorvastatin 10mg
            - Simvastatin 10mg

- Lovastatin 20mg
- Pravastatin 40mg
- Fluvastatin 40mg
- Pitavastatin 2mg

- One statin at any daily dose

Approval will be for **12 months**

B. Nexletol (bempedoic acid) and Nexlizet (bempedoic acid and ezetimibe) may be considered **medically necessary** for the treatment of **heterozygous familial hypercholesterolemia (HeFH)** when the following criteria are met:

1. Patient is 18 years of age or older
2. Patient has a definite diagnosis of HeFH, which is confirmed by ONE of the following:
   a). An LDL-receptor mutation, familial defective apo B-100, or a PCSK9 gain-of-function mutation; **OR**
   b). Definite FH per Simon-Broome Diagnostic Criteria or Dutch Lipid Network Criteria (Appendix C)
3. Patient is engaging in aggressive lifestyle modifications (Appendix B)
4. Patient has been unable to achieve an LDL-C of < 100 mg/dL (or ≤ 70 mg/dL with clinical atherosclerotic cardiovascular disease [ASCVD]) despite adherence to the combination of lifestyle changes and at least three months of ALL the following lipid lowering therapy:
   a). A trial of BOTH high-intensity statins (atorvastatin 40-80 mg and rosuvastatin 20-40 mg) at a maximum tolerated dose in combination with ezetimibe
   OR
   A trial of TWO moderate intensity statins (e.g. pravastatin 40-80 mg, lovastatin 40 mg, fluvastatin 80 mg, pitavastatin 2-4 mg, simvastatin 20-40 mg) in combination with ezetimibe, only in the event the patient is unable to complete either of the high-intensity statin trials at the maximum approved dosing AND
   b). A trial of PCSK9-targeted therapy
5. Nexletol will be added to statin and ezetimibe therapy or Nexlizet will be added to statin therapy

OR

1. Patient is 18 years of age or older
2. Patient has a definite diagnosis of HeFH, which is confirmed by ONE of the following:
   a). An LDL-receptor mutation, familial defective apo B-100, or a PCSK9 gain-of-function mutation; **OR**
   b). Definite FH per Simon-Broome Diagnostic Criteria or Dutch Lipid Network Criteria (Appendix C)
3. Patient is engaging in aggressive lifestyle modifications (Appendix B)
4. Patient has a documented contraindication (e.g., active liver disease, pregnancy, breastfeeding), or medically justifiable reason that precludes statin use (e.g. patients has experienced rhabdomyolysis, CK elevations ≥ 10x ULN, or statin intolerance).
   a). Statin intolerance shall be defined in accordance with the National Lipid Association definition:
      i. Inability to tolerate at least two statins (one at any dose, one at lowest daily dose) due to objectionable symptoms or abnormal biomarkers temporally related to statin use, reversible upon statin discontinuation and reproducible by re-challenge while excluding other known determinants. Other known determinants include low body mass index (BMI), acute infection, untreated or undertreated hypothyroidism, severe renal or

hepatic dysfunction, organ transplant, recent severe trauma, HIV infection, Vitamin D deficiency, history of creatine kinase elevation, history of preexisting or unexplained muscle or joint pain, high level of physical activity, illicit drug abuse, excess alcohol use. Each statin trial, both initial and re-challenge shall be at least two weeks duration.

- A trial of one statin at lowest starting daily dose
  - Rosuvastatin 5mg
  - Atorvastatin 10mg
  - Simvastatin 10mg
  - Lovastatin 20mg
  - Pravastatin 40mg
  - Fluvastatin 40mg
  - Pitavastatin 2mg
- One statin at any daily dose

5. Patient has been unable to achieve an LDL-C of< 100 mg/dL (or ≤ 70 mg/dL with clinical atherosclerotic cardiovascular disease [ASCVD]) despite adherence to the combination of lifestyle changes and at least a three-month trial of PCSK9-targeted therapy

Approval will be for **12 months**

Continuation of Therapy

A. The continuation of therapy for either Nexletol or Nexlizet may be considered **medically necessary** for the treatment of **clinical atherosclerotic cardiovascular disease (ASCVD)** when all the following criteria are met:
   1. Patient has had a reduction or maintained a reduction in LDL-C
   2. Patient continues to receive concomitant maximally tolerated statin therapy (unless contraindicated or not tolerated)
   3. Patient continues to receive concomitant ezetimibe therapy (unless contraindicated or not tolerated)
   4. Patient continues to demonstrate adherence with ACL inhibitor, statin therapy, and lifestyle modifications

Approval will be for **12 months**

B. The continuation of therapy for either Nexletol or Nexlizet may be considered **medically necessary** for the treatment of **heterozygous familial hypercholesterolemia (HeFH)** when all the following criteria are met:
   1. Patient has had a reduction or maintained a reduction in LDL-C
   2. Patient continues to receive concomitant maximally tolerated statin therapy (unless contraindicated or not tolerated)
   3. Patient continues to receive concomitant ezetimibe therapy (unless contraindicated or not tolerated)
   4. Patient continues to receive concomitant PCSK9-targeted therapy
   5. Patient continues to demonstrate adherence with ACL inhibitor, statin therapy, PCSK9-targeted therapyand lifestyle modifications

Approval will be for **12 months**

The aforementioned drugs are considered **not medically necessary** for patients who do not meet the criteria set forth above.

Dosage and Administration

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

Quantity Limits

- Nexletol 180 mg –30 tablets per 30 days
- Nexlizet 180mg/10mg – 30 tablets per 30 days

APPENDIX

APPENDIX A: Clinical Atherosclerotic Cardiovascular Disease (ASCVD)

Clinical atherosclerotic cardiovascular disease (ASCVD) includes acute coronary syndrome (ACS), those with history of myocardial infarction (MI), stable or unstable angina or coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral arterial disease (PAD) including aortic aneurysm, all of atherosclerotic origin.

APPENDIX B: Aggressive Lifestyle Modifications

Aggressive lifestyle modifications comprise of healthy lifestyle changes including the following:

- A healthy-fat diet (saturated fat <10% of total calories) emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish
- An exercise program (150 minutes or more of moderate to vigorous intensity physical activity per week, or engaging as medically appropriate)

APPENDIX C: Diagnosis of definite familial hypercholesterolemia (FH)

1. Simon-Broome Diagnostic Criteria for definite FH
   a) Total cholesterol > 290 mg/dL or LDL-C > 190 mg/dL in patients over 16 years of age or total cholesterol > 260 mg/dL or LDL-C > 155 mg/dL in patients less than 16 years of age
   AND
   b) Tendon xanthomas in the patient, first (parent, sibling or child) or second degree relative (grandparent, uncle or aunt)
2. Dutch Lipid Clinic Network Criteria for definite FH
   a) Total score > 8 points

CLINICAL RATIONALE

Nexletol is an adenosine triphosphate-citrate lyase (ACL) inhibitor that inhibits cholesterol synthesis in the liver and thereby lowers LDL-C. ACL is an enzyme upstream of 3-hydrox-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase in the cholesterol synthesis pathway. Inhibiting ACL results in decreased cholesterol synthesis in the liver and lowers LDL-C in blood via upregulation of low-density lipoprotein receptors.

Efficacy

The efficacy and safety of bempedoic acid was assessed in four phase III trials: CLEAR Harmony, CLEAR Wisdom, CLEAR Serenity, and CLEAR Tranquility. CLEAR Harmony and CLEAR Wisdom were both phase III, multi-center, randomized, double-blind, placebo-controlled 52 week trials that enrolled adult patients with heterozygous familial hypercholesterolemia and/or established atherosclerotic cardiovascular disease whose LDL levels were not adequately controlled on maximally tolerated statin therapy.

In CLEAR Harmony, the overall mean age at baseline was 66 years (range: 24 to 88 years). 95% of patients had established atherosclerotic cardiovascular disease, and 5% of patients had HeFH. The mean baseline LDL-C was 103.2 mg/dL. Patients were followed for 52 weeks with lipid panels done at week 4, 8, 12, 24, 36 and 52. The primary efficacy outcome measure of the study was the percent change from baseline to Week 12 in LDL-C. The difference between Nexletol and placebo in mean percent change in LDL-C from baseline to Week 12 was -18% (95% CI: -20%, -16%; $p < 0.001$). High-density lipoprotein (HDL) and triglycerides (TG) were examined as exploratory endpoints and were not included in the statistical hierarchy. The difference between Nexletol and placebo in mean percent change from baseline to Week 12 was -6% for HDL and median percent change from baseline to Week 12 was +3% for TG.

In CLEAR Wisdom, the overall mean age at baseline was 64 years (range: 28 to 91 years). 95% of patients had established atherosclerotic cardiovascular disease, and 5% of patients had HeFH. The mean baseline LDL-C was 120.4 mg/dL. Patients were followed for 52 weeks with lipid panels done at week 4, 12, 24, and 52. The primary efficacy outcome measure of the study was the percent change from baseline to Week 12 in LDL-C. The difference between NEXLETOL and placebo in mean percent change in LDL-C from baseline to Week 12 was -17 % (95% CI: -21%, -14%; $p < 0.001$). HDL and TG were exploratory endpoints and not included in the statistical hierarchy. The difference between Nexletol and placebo in mean percent change from baseline to Week 12 was -6% for HDL and the median percent change from baseline was -2% for TG.

CLEAR Serenity was a phase III, double-blind, placebo-controlled study that randomized 345 patients with hypercholesterolemia and a history of intolerance to at least 2 statins (1 at the lowest available dose) that still required additional lipid-lowering for primary or secondary prevention of CV events. Patients were randomized 2:1 to bempedoic acid 180 mg or placebo once daily for 24 weeks. The primary end point was mean percent change from baseline to week 12 in low-density lipoprotein cholesterol. The mean age was 65.2 years, mean baseline low-density lipoprotein cholesterol was 157.6 mg/dL, and 93% of patients reported a history of statin-associated muscle symptoms. Nexletol treatment significantly reduced low-density lipoprotein cholesterol from baseline to week 12 (placebo-corrected difference, -21.4% [95% CI, -25.1% to -17.7%]; $P<0.001$). Significant reductions with Nexletol versus placebo were also observed in non-high-density lipoprotein cholesterol (-17.9%), total cholesterol (-14.8%), apolipoprotein B (-15.0%), and high-sensitivity C-reactive protein (-24.3%; $P<0.001$ for all comparisons).

CLEAR Tranquility was a phase III, multinational, randomized, double-blind, placebo-controlled, 12 week trial that studied the combination of Nexletol (bempedoic acid) and Zetia (ezetimibe) in patients with a history of statin intolerance and an LDL-C ≥ 100 mg/dL while receiving stable lipid-lowering therapy. In general, the study population demographics were similar to the Nexletol trials; the mean baseline LDL-C level was 129.8 mg/dL for the Nexletol arm. During the run-in phase, all patients received open-label Zetia to confirm tolerance to Zetia. At the double-blind treatment phase, patients were randomized to receive Nexletol or placebo for 12 weeks while the open-label Zetia treatment was maintained throughout the study. The addition of Nexletol to Zetia achieved a placebo-adjusted reduction in LDL-C of 28.5% (95% confidence interval -34.4 to -22.5; $p < 0.001$) to a mean LDL-C level of 96.2 mg/dL at 12 weeks. Significant reductions in secondary endpoints, including non-high-density lipoprotein cholesterol (-23.6%), total cholesterol (-18.0%), apolipoprotein B (-19.3%), and high-sensitivity C-reactive protein (-31.0%) , were observed with Nexletol vs. placebo ($p < 0.001$).

A cardiovascular outcomes trial (CLEAR Outcomes) is currently underway. The primary of endpoint of the study is the effect on bempedoic acid on major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization). The trial is expected to conclude in 2022.

Safety

In clinical trials, there was no significant difference between Nexletol and placebo in the rates of major cardiovascular AEs including CV death, nonfatal MI, nonfatal stroke, coronary revascularization, hospitalization due to unstable angina, death from non-CV cause, non-coronary arterial revascularization, and hospitalization due to heart failure. The most common reasons for Nexletol treatment discontinuation were muscle spasms (0.5% vs 0.3% placebo), diarrhea (0.4% vs 0.1% placebo), and pain in extremity (0.3% vs. 0% placebo). The most common adverse reactions (incidence ≥ 2% and greater than placebo) were upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anemia, and elevated liver enzymes. Nexletol was associated with an increased risk of tendon rupture and gout. Concomitant use of Nexletol with simvastatin at a dose greater than 20 mg or pravastatin at a dose greater than 40 mg should be avoided due to an increased risk of statin-related myopathy. Nexlizet safety outcomes were similar to findings from the Nexletol trials.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD-CM diagnostic codes.

- N/A

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POLICY HISTORY

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