INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer’s particular benefit plan document (Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document) may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer’s benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer’s benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

Bempedoic acid (Nexletol™) is considered medically necessary when ALL of the following criteria are met:

- Individual is 18 years of age or older
- When used for ONE of the following indications:
  - **Atherosclerotic Cardiovascular Disease (ASCVD)** when ALL of the following criteria are met:
    - Individual has a confirmed diagnosis of established ASCVD as evidenced by ONE of the following:
      - Coronary heart disease (acute coronary syndromes, history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization)
      - Cerebrovascular disease (stroke, transient ischemic attack)
      - Peripheral arterial disease (PAD) of atherosclerotic origin
    - Use is adjunctive to maximally tolerated statin therapy unless contraindicated per FDA label or intolerant. *NOTE: For statin intolerant individuals, see box below for additional criteria related to preferred products.*
    - The individual has had an inadequate response to therapy as defined by the use of one high-intensity statin therapy (for example: atorvastatin ≥ 40 mg daily; rosvastatin ≥ 20 mg
daily) OR maximally tolerated statin if documented intolerance to high intensity statin, **AND** ezetimibe (unless contraindicated per FDA label or intolerant) concomitantly for ≥ 8 continuous weeks **AND** the low-density lipoprotein cholesterol level after this treatment regimen remains ≥ 70 mg/dL

- **Heterozygous Familial Hypercholesterolemia (HeFH)** when **ALL** of the following criteria are met:
  - Individual has a confirmed diagnosis of HeFH as defined by **ONE** of the following:
    - WHO Criteria (Dutch Lipid Network clinical criteria, score greater than 5; see [Appendix 1](#))
    - Simon-Broome Criteria (threshold met for “definite” or “possible” familial hypercholesterolemia, see [Appendix 2](#))
    - Confirmed genetic testing
    - LDL-C ≥ 190 mg/dL (prior to treatment with antihyperlipidemic agents)
    - Clinical manifestations of HeFH (e.g., cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma)
  - Use is adjunctive to maximally tolerated statin therapy unless contraindicated per FDA label or intolerant. *NOTE*: For statin intolerant individuals, see box below for additional criteria related to preferred products.
  - The individual has had an inadequate response to therapy as defined by the use of one high-intensity statin therapy (for example: atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily) OR maximally tolerated statin if documented intolerance to high intensity statin, **AND** ezetimibe (unless contraindicated per FDA label or intolerant) concomitantly for ≥ 8 continuous weeks **AND** the low-density lipoprotein cholesterol level after this treatment regimen remains ≥ 70 mg/dL

**Bempedoic acid/ezetimibe (Nexlizet™)** is considered medically necessary when **ALL** of the following criteria are met:
- Individual is 18 years of age or older
- When used for **ONE** of the following indications:
  - **Atherosclerotic Cardiovascular Disease (ASCVD)** when **ALL** of the following criteria are met:
    - Individual has a confirmed diagnosis of established ASCVD as evidenced by **ONE** of the following:
      - Coronary heart disease (acute coronary syndromes, history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization)
      - Cerebrovascular disease (stroke, transient ischemic attack)
      - Peripheral arterial disease (PAD) of atherosclerotic origin
    - Use is adjunctive to maximally tolerated statin therapy unless contraindicated per FDA label or intolerant. *NOTE*: For statin intolerant individuals, see box below for additional criteria related to preferred products.
    - The individual has had an inadequate response to therapy as defined by the use of one high-intensity statin therapy (for example: atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily) OR maximally tolerated statin if documented intolerance to high intensity statin, for ≥ 8 continuous weeks **AND** the low-density lipoprotein cholesterol level after this treatment regimen remains ≥ 70 mg/dL
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      - WHO Criteria (Dutch Lipid Network clinical criteria, score greater than 5; see [Appendix 1](#))
      - Simon-Broome Criteria (threshold met for “definite” or “possible” familial hypercholesterolemia, see [Appendix 2](#))
- Confirmed genetic testing
- LDL-C ≥ 190 mg/dL (prior to treatment with antihyperlipidemic agents)
- Clinical manifestations of HeFH (e.g., cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma)

- Use is adjunctive to maximally tolerated statin therapy unless contraindicated per FDA label or intolerant. *NOTE: For statin intolerant individuals, see box below for additional criteria related to preferred products.
- The individual has had an inadequate response to therapy as defined by the use of one high-intensity statin therapy (for example: atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily) OR maximally tolerated statin if documented intolerance to high intensity statin, for ≥ 8 continuous weeks AND the low-density lipoprotein cholesterol level after this treatment regimen remains ≥ 70 mg/dL.

Coverage for bempedoic acid (Nexletol™) and bempedoic acid/ezetimibe (Nexlizet™) varies across plans. Refer to the customer's benefit plan document for coverage details.

Where coverage requires the use of preferred products, the following conditions of coverage apply in addition to the criteria listed above.

For Employer Group Plans:

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<tbody>
<tr>
<td>Nexletol™ (bempedoic acid)</td>
<td>For statin intolerant individuals:</td>
<td>Documented intolerance to EITHER atorvastatin or rosvastatin with symptoms or abnormal lab results resolving upon discontinuation of statin therapy and other causes being ruled out</td>
<td>For statin intolerant individuals ALL of the following:</td>
<td>Documented intolerance to BOTH atorvastatin and rosvastatin with symptoms or abnormal lab results resolving upon discontinuation of statin therapy and other causes being ruled out</td>
<td>Documented failure/inadequate response, contraindication per FDA label, intolerance, or inability to use a PCSK9 inhibitor (such as Repatha or Praluent)</td>
</tr>
<tr>
<td>Nexlizet™ (bempedoic acid/ezetimibe)</td>
<td>For statin intolerant individuals:</td>
<td>Documented intolerance to EITHER atorvastatin or rosvastatin with symptoms or abnormal lab results resolving upon discontinuation of statin therapy and other causes being ruled out</td>
<td>For statin intolerant individuals ALL of the following:</td>
<td>Documented intolerance to BOTH atorvastatin and rosvastatin with symptoms or abnormal lab results resolving upon discontinuation of statin therapy and other causes being ruled out</td>
<td>Documented failure/inadequate response, contraindication per FDA label, intolerance, or inability to use a PCSK9 inhibitor (such as Repatha or Praluent)</td>
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Initial authorization is up to 12 months.
Bempedoic acid (Nexletol™) and bempedoic acid/ezetimibe (Nexlizet™) are considered medically necessary for continued use when ALL of the following criteria are met:

- Initial criteria listed above are met
- Documented evidence of beneficial clinical response (for example, demonstrated reduction of LDL-C)

Reauthorization is up to 12 months.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Bempedoic acid (Nexletol™) and bempedoic acid/ezetimibe (Nexlizet™) are considered experimental, investigational or unproven for ANY other use.

Note: Receipt of sample product does not satisfy any criteria requirements for coverage

**FDA Approved Indications**

**FDA Approved Indication**
Nexletol™ and Nexlizet™ are indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL-C.

**Limitations of Use:** The effect of Nexletol™ and Nexlizet™ on cardiovascular morbidity and mortality have not been determined.

**Recommended Dosing**

**FDA Recommended Dosing**
The recommended dosage of Nexletol™, in combination with maximally tolerated statin therapy, is 180 mg administered orally once daily. Nexletol™ can be taken with or without food.

The recommended dosage of Nexlizet™, in combination with maximally tolerated statin therapy, is one tablet orally once daily. One tablet of Nexlizet™ contains 180 mg of bempedoic acid and 10 mg of ezetimibe. Swallow the tablet whole. Nexlizet™ can be taken with or without food.

After initiation of Nexletol™ or Nexlizet™, analyze lipid levels within 8 to 12 weeks.

**General Background**

**Disease Overview**
ASCVD (including CV disease) is a leading cause of morbidity and mortality worldwide. 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, or peripheral arterial disease. 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). In 2017, CV disease was listed as the underlying cause of death in approximately 859,125 US patients. In 2017, CHD was the leading cause of death attributable to CV disease in the US (42.6%), followed by stroke (17.0%), high blood pressure (10.5%), heart failure (9.4%), diseases of the
arteries (2.9%) and other CV diseases (17.6%). When considered independently from CV disease, stroke led to 146,383 US deaths in 2017. (Grundy, 2018; Stone, 2013)

Familial hypercholesterolemia is an autosomal dominant genetic disease that is noted by markedly elevated LDL-C, often at a young age, and premature ASCVD. 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 Broom 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. (Gidding, 2015; Goldberg, 2011; McGowan, 2019)

Professional Societies/Organizations
Many guidelines are available regarding the treatment of patients with dyslipidemia which include the management of HeFH and ASCVD. 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%. Other statin regimens, including atorvastatin and rosuvastatin at lower doses are classified as moderate-intensity (LDL-C reductions of 30% to 49%) products and low-intensity agents (LDL-C reductions < 30%). (Gidding, 2015; Goldberg, 2011; Grundy, 2018; McGowan, 2019)

The American Heart Association (AHA)/American College of Cardiology (ACC)
The American Heart Association (AHA)/American College of Cardiology (ACC) guidelines on the management of blood cholesterol (2018) defines ACSVD as ACS, those with a history of MI, stable or unstable angina or coronary or other revascularizations, stroke, transient ischemic attack (TIA), or peripheral arterial disease (PAD). An LDL-C < 70 mg/dL is recommended in for most patients with ASCVD to reduce CV risk. In 2015, the AHA published a scientific statement regarding familial hypercholesterolemia. 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%. Statins are the initial treatment for all adults with familial hypercholesterolemia. High- or moderate-intensity statins are recommended; low potency statins are generally inadequate for patients with familial hypercholesterolemia due to the markedly elevated LDL-C levels. If LDL-C does not reach the desired goal or percentage decrease, ezetimibe is recommended to be added to statin therapy. Three drug combinations incorporating a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor, a bile acid sequestrant (colesevelam), or niacin is also recommended. For patients with HoFH, the addition of other therapies (e.g., Juxtapid® [lomitapide capsules], low-density lipoprotein apheresis) may be added. In patients with HeFH who have not yet manifested ASCVD, LDL-C levels ≤ 100 mg/dL are recommended. (AHA, 2020; Stone, 2013)

In 2019, the AHA issued a scientific statement regarding statin safety and associated adverse events.(Newman, 2019) In general, statins are well-tolerated agents that have successfully led to decreased LDL-C levels which led to reductions in CV events (e.g., MI, ischemic stroke). The risk of serious statin-induced muscle injury (e.g., rhabdomyolysis) is low (< 0.01%). In US clinical practice, about 10% of patients stop taking statin therapy due to subjective complaints, of which muscle symptoms without significantly raised CK levels are noted. Data suggests that the muscle symptoms that occur among patients are not caused by the pharmacologic effects of the statin and restarting statin therapy for these patients is important, especially among patients at high risk of
CV events, for whom CV event prevention is important. Several studies have shown that patients were believing that they were “statin intolerant”. However, many patients were able to subsequently tolerate a statin upon rechallenge and receive the benefits provided with these agents. Other data supports this occurrence. (Moriarty, 2015; Zhang, 2013; Mampuya, 2013)

The American Board of Internal Medicine’s (ABIM) Foundation Choosing Wisely® Initiative:
No recommendations are available for bempedoic acid.

Other Uses with Supportive Evidence
AHFS Drug Information 2020 Edition does not support any off-label uses of bempedoic acid.

Experimental, Investigational, Unproven Uses
Compendia and other published clinical studies do not currently support any uses other than the FDA indication. Criteria will be updated as new published data are available.

APPENDIX 1 – WHO Criteria (Dutch Lipid Network Clinical Criteria) for Diagnosis of Heterozygous Familial Hypercholesterolemia (HeFH) (Nordestgaard, 2013)

<table>
<thead>
<tr>
<th>Diagnostic Scoring for Heterozygous Familial Hypercholesterolemia</th>
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<tbody>
<tr>
<td><strong>Family History</strong></td>
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<tr>
<td>First degree relative with known premature (men &lt; 55 yrs, women &lt; 60 yrs) coronary vascular disease</td>
</tr>
<tr>
<td>First degree relative with known LDL-cholesterol &gt;95th percentile for age and sex and/or</td>
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<tr>
<td>First degree relative with tendon xanthomata and/or arcus cornaeals</td>
</tr>
<tr>
<td>Children below 18 yrs with LDL-cholesterol &gt;95th percentile for age and sex</td>
</tr>
<tr>
<td><strong>Clinical History</strong></td>
</tr>
<tr>
<td>Patient has premature (men &lt; 55 yrs, women &lt; 60 yrs) coronary artery disease</td>
</tr>
<tr>
<td>Patient has premature (men &lt; 55 yrs, women &lt; 60 yrs) cerebral or peripheral vascular disease</td>
</tr>
<tr>
<td><strong>Physical Examination</strong></td>
</tr>
<tr>
<td>Tendon xanthomata</td>
</tr>
<tr>
<td>Arcus cornaeals below the age of 45 yrs</td>
</tr>
<tr>
<td><strong>Laboratory Analysis</strong></td>
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<tr>
<td>LDL-cholesterol</td>
</tr>
<tr>
<td>&gt; 8.5</td>
</tr>
<tr>
<td>6.5 – 8.4</td>
</tr>
<tr>
<td>5.0 – 6.4</td>
</tr>
<tr>
<td>4.0 – 4.9</td>
</tr>
<tr>
<td>(HDL-cholesterol and triglycerides are normal)</td>
</tr>
<tr>
<td><strong>DNA Analysis</strong></td>
</tr>
<tr>
<td>Functional mutation low-density lipoprotein receptor gene present</td>
</tr>
<tr>
<td><strong>Diagnosis of HeFH is:</strong></td>
</tr>
<tr>
<td>Certain When</td>
</tr>
<tr>
<td>Probable When</td>
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<tr>
<td>Possible When</td>
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</table>
APPENDIX 2 – Simon Broome Register Diagnostic Criteria for Heterozygous Familial Hypercholesterolemia (HeFH) (Scientific Steering Committee, 1991)

**Definite familial hypercholesterolemia is defined as:**
- Total cholesterol > 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. (Levels either pre-treatment or highest on treatment)

PLUS
- Tendon xanthomas in patient or in 1st degree relative (parent, sibling, child), or in 2nd degree relative (grandparent, uncle, aunt)

OR
- DNA-based evidence of an LDL receptor mutation or familial defective apo B-100

**Possible familial hypercholesterolemia is defined as:**
- Total cholesterol > 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. (Levels either pre-treatment or highest on treatment)

And at least one of the following:
- Family history of myocardial infarction below 50 years of age in 2nd degree relative or below 60 years of age in 1st degree relative.
- Family history of raised cholesterols > 7.5 mmol/L (290 mg/dL) in adult 1st or 2nd degree relative or > 6.7 mmol/L (260 mg/dL) in child or sibling under 16 years of age.

**Coding/Billing Information**

Note: Bempedoic acid and bempedoic acid/ezetimibe are typically covered under pharmacy benefit plans. Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed. Medical drug coding and diagnosis codes, however, are generally not required for pharmacy claims submissions, therefore, this section is not in use.

**References**