Cigna National Preferred Formulary Coverage Policy

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Prior Authorization
Hyperlipidemia – Nexletol™ (bempedoic acid tablets)

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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.

NPF Coverage Policy

Cigna covers bempedoic acid (Nexletol™) as medically necessary when the following criteria are met for FDA Indications or Other Uses with Supportive Evidence:

Prior authorization is recommended for prescription benefit coverage of Nexletol. All approvals are provided for the duration noted below.

FDA Indication(s)

1. **Atherosclerotic Cardiovascular Disease (ASCVD).** Approve for 1 year if the individual meets the following criteria (A, B, and C):
   - **A)** The individual is ≥ 18 years of age; AND
   - **B)** The individual has had one of the following conditions or diagnoses (i, ii, iii, iv or v):
     - **i.** The individual has had a previous myocardial infarction or has a history of an acute coronary syndrome; OR
     - **ii.** The individual has a diagnosis of angina (stable or unstable); OR

iii. The individual has a past history of stroke or transient ischemic attack; OR
iv. The individual has peripheral arterial disease; OR
v. The individual has undergone a coronary or other arterial revascularization procedure in the past (e.g., coronary artery bypass graft, percutaneous coronary intervention, angioplasty, coronary stent procedure); AND

C) The individual meets one of the following criteria (i or ii):
i. The individual meets both of the following criteria (a and b):
a) The individual 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 ezetimibe (as a single-entity or as a combination product) concomitantly for ≥ 8 continuous weeks; AND
b) The low-density lipoprotein cholesterol level after this treatment regimen remains ≥ 70 mg/dL; OR
ii. The individual has been determined to be statin intolerant by meeting one of the following criteria (a or b):
a) The individual experienced statin-related rhabdomyolysis (Note: Statin-induced muscle breakdown that is usually 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
b) The individual experienced skeletal-related muscle symptoms (e.g., myopathy [muscle weakness] or myalgia [muscle aches, soreness, stiffness, or tenderness]) and meets both of the following criteria [(1) and (2)]:
(1) The skeletal-related muscle symptoms (e.g., myopathy or myalgia) occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND
(2) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms (e.g., myopathy, myalgia) resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin).

2. Heterozygous Familial Hypercholesterolemia (HeFH). Approve for 1 year if the individual meets the following criteria (A, B, and C):
A) The individual is ≥ 18 years of age; AND
B) The individual meets one of the following criteria (i, ii, iii, or iv):
i. The individual has an untreated low-density lipoprotein cholesterol (LDL-C) level ≥ 190 mg/dL (prior to treatment with antihyperlipidemic agents); OR
ii. The individual 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
iii. The individual has been diagnosed with HeFH meeting one of the following diagnostic criteria thresholds (a or b):
a) The prescriber used the Dutch Lipid Network criteria and the individual has a score > 5; OR
b) The prescriber used the Simon Broome criteria and the individual met the threshold for “definite” or “possible” familial hypercholesterolemia; OR
iv. The individual has clinical manifestations of HeFH (e.g., cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma); AND
C) The individual meets one of the following criteria (i or ii):
i. The individual meets both of the following criteria (a and b):

a) The individual 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 ezetimibe (as a single-entity or as a combination product) concomitantly for ≥ 8 continuous weeks; AND

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

ii. The individual has been determined to be statin intolerant by meeting one of the following criteria (a or b):

a) The individual experienced statin-related rhabdomyolysis (Note: Statin-induced muscle breakdown that is usually 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

b) The individual experienced skeletal-related muscle symptoms (e.g., myopathy [muscle weakness] or myalgia [muscle aches, soreness, stiffness, or tenderness]) and meets both of the following criteria [(1) and (2)]:

(1) The skeletal-related muscle symptoms (e.g., myopathy or myalgia) occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND

(2) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms (e.g., myopathy, myalgia) resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin).

Conditions Not Covered

Bempedoic acid (Nexletol™) is considered experimental, investigational or unproven for ANY other use.

Background

Overview

Nexletol, an adenosine triphosphate-citrate lyase inhibitor, is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of heterozygous familial hypercholesterolemia (HeFH) or established atherosclerotic cardiovascular disease (ASCVD) in adults who require additional lowering of low-density lipoprotein cholesterol (LDL-C). Limitations of Use. The effect of Nexletol on cardiovascular (CV) morbidity and mortality have not been established.

Disease Overview

ASCVD (including CV disease) is a leading cause of morbidity and mortality worldwide.[2-4] ASCVD is defined as individuals 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.[3,4] Lowering LDL-C levels has been strongly correlated to reduce the risk of subsequent CV disease among individuals 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 individuals.[2] In 2017, CHD was the leading causes 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.

Familial hypercholesterolemia is an autosomal dominant genetic disease that is noted by markedly elevated LDL-C, often at a young age, and premature ASCVD.[5-8] The condition is often undiagnosed and untreated. It is estimated that 620,000 individuals 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 individuals. 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 individuals 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. Individuals 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 individuals with statins recommended as first-line. Other therapies are also added to reduce LDL-C.

Guidelines

Many guidelines are available regarding the treatment of individuals with dyslipidemia which include the management of HeFH and ASCVD.[3-5,9-12] For individuals 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%). 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).[2,3] An LDL-C < 70 mg/dL is recommended in for most individuals 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 individuals 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 individuals with HoFH, the addition of other therapies (e.g., Juxtapid® [lomitapide capsules], low-density lipoprotein apheresis) may be added. In individuals with HeFH who have not yet manifested ASCVD, LDL-C levels ≤ 100 mg/dL are recommended.

In 2019 the AHA issued a scientific statement regarding statin safety and associated adverse events.[12] 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 individuals 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 individuals are not caused by the pharmacologic effects of the statin and restarting statin therapy for these individuals is important, especially among individuals at high risk of CV events, for whom CV event prevention is important. Several studies have shown that individuals were believing that they were “statin intolerant”. However, many individuals were able to subsequently tolerate a statin upon rechallenge and receive the benefits provided with these agents. Other data supports this occurrence.[13-16]

Safety

Warnings/Precautions include hyperuricemia and an increased risk of tendon rupture.[1]

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Last Revision Details

Update	3/25/2020: No criteria changes. For the diagnosis of ASCVD and HeFH, the criteria question was broken up into two sections as follows: **C.i.** The individual meets both of the following criteria (a and b): **a)** The individual 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 ezetimibe (as a single-entity or as a combination product) concomitantly for ≥ 8 continuous weeks; AND **b)** The LDL-C level after this treatment regimens remains ≥ 70 mg/dL.	3/25/20

ASCVD – Atherosclerotic cardiovascular disease; HeFH – Heterozygous familial hypercholesterolemia; LDL –C – Low-density lipoprotein cholesterol.

APPENDIX A.
Simon Broome Register Diagnostic Criteria[15]

Definite Familial Hypercholesterolemia:
a) Raised cholesterol
   (i) 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;
   (ii) 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);
b) AND
   (i) Tendon xanthomas in the individual or in a first (parent, sibling, or child) or second-degree relative (grandparent, aunt, or uncle);
c) OR
   (i) DNA-based evidence of LDL-receptor, familial defective apo B-100, or PCSK9 mutation.

Possible Familial Hypercholesterolemia:
a) Raised cholesterol
   (i) 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;
   (ii) Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult;
b) AND at least one of the following:
   (i) 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;
c) OR
   (i) 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.

APPENDIX B.
Dutch Lipid Network Criteria for Familial Hypercholesterolemia[16]

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	
Individual with premature CAD (age as above)	2
Individual 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.

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