# LOUISIANA **BLUE** 🕸 🥘

# bempedoic acid Products (Nexletol<sup>TM</sup>, Nexlizet<sup>TM</sup>)

Policy # 00714 Original Effective Date: 12/14/2020 Current Effective Date: 01/13/2025

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

# When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member's contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider bempedoic acid products (Nexletol, Nexlizet)<sup>M</sup><sup>‡</sup> to be **eligible for coverage**<sup>\*\*</sup> when the patient selection criteria are met.

#### Patient Selection Criteria

Coverage eligibility will be considered for bempedoic acid products (Nexletol, Nexlizet) when the following criteria are met:

- I. Patient is 18 years of age or older; AND
- II. Patient is compliant with any medications required for therapy prior to receiving authorization for bempedoic acid products (Nexletol, Nexlizet); AND
- III. bempedoic acid products (Nexletol, Nexlizet) will NOT be used in combination with lomitapide (Juxtapid<sup>®</sup>)<sup>‡</sup>, mipomersen (Kynamro<sup>®</sup>)<sup>‡</sup>, evolocumab (Repatha<sup>™</sup>)<sup>‡</sup>, or alirocumab (Praluent<sup>®</sup>)<sup>‡</sup>; AND
- IV. bempedoic acid products (Nexletol, Nexlizet) will be used along with a maximally tolerated statin [in those who are not considered statin intolerant (see below for statin intolerance)]; AND
- V. Patient must meet one of the following (A, B, C, or D):
  - A. Patient has a diagnosis of Familial Hypercholesterolemia (FH) withOUT clinical atherosclerotic cardiovascular disease, defined as a WHO (World Health Organization)/Dutch Lipid Clinic Network score of >8; AND
    - i. Patient's low density lipoprotein cholesterol (LDL-C) is not adequately controlled [e.g., not at the LDL-C treatment goal for a "high risk" (LDL-C goal <100 mg/dL) or "very high risk" (LDL-C goal <70 mg/dL) patient based on the current National Lipid Association (NLA) guidelines and the patient's specific characteristics] with a high intensity statin [rosuvastatin (Crestor<sup>®</sup>)<sup>‡</sup> 20-40 mg, atorvastatin (Lipitor<sup>®</sup>)<sup>‡</sup> 40-80 mg] PLUS ezetimibe (Zetia<sup>®</sup>)<sup>‡</sup> 10 mg daily for at least 3 months (*Note that the 3 month timeframe and the addition of ezetimibe* (Zetia) are additional company requirements and will be denied as not medically necessary\*\* if not met); OR

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield Association. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana. (© 2024 Louisiana Blue

Policy # 00714 Original Effective Date: 12/14/2020 Current Effective Date: 01/13/2025

- ii. Patient's LDL-C is not adequately controlled [e.g., not at the LDL-C treatment goal for a "high risk" (LDL-C goal <100 mg/dL) or "very high risk" (LDL-C goal <70 mg/dL) patient based on the current NLA guidelines and the patient's specific characteristics] with a maximally tolerated stable daily statin (of any potency) PLUS ezetimibe (Zetia) 10 mg daily for at least 3 months ONLY if proof is given that a high potency maximum daily dose statin was not well tolerated (*Note that the 3 month timeframe and the addition of ezetimibe* (Zetia) are additional company requirements and will be denied as not medically necessary\*\* if not met); OR
- B. Patient has a diagnosis of FH withOUT clinical atherosclerotic cardiovascular disease, defined as a WHO/Dutch Lipid Clinic Network score of >8; AND
  - i. Patient's LDL-C is not adequately controlled [e.g., not at the LDL-C treatment goal for a "high risk" (LDL-C goal <100 mg/dL) or "very high risk" (LDL-C goal <70 mg/dL) patient based on the current NLA guidelines and the patient's specific characteristics] due to statin intolerance; AND
  - ii. Patient must meet ALL of the following criteria to be considered statin intolerant:
    - Patient was unable to tolerate at least 2 different statins. [The inability to tolerate one statin will be accepted if the patient experienced rhabdomyolysis or clinically-significant myonecrosis secondary to a statin. Rhabdomyolysis/myonecrosis is considered to be a muscle breakdown with signs and symptoms such as muscle pain, weakness, tenderness ALONG WITH either: a.) acute renal failure or myoglobinuria AND elevated creatine kinase levels (e.g., ≥ 10 times the upper limit of normal) OR b.) elevated creatine kinase levels (e.g., ≥ 10 times the upper limit of normal) alone]; AND
    - 2. Patient's intolerance was associated with confirmed, intolerable statin-related adverse effects [e.g., skeletal related muscle symptoms (myopathy [muscle weakness] or myalgia [muscle aches, soreness, stiffness, or tenderness])]; AND
    - 3. Patient's symptoms or biomarker changes resolved or showed significant improvement on dose decrease or discontinuation; OR
- C. Patient has the presence of clinical atherosclerotic cardiovascular disease (either FH or non-FH); AND
  - i. Patient's LDL-C is not adequately controlled [e.g., not at the LDL-C treatment goal of <70 mg/dL based on the current NLA guidelines] with a high intensity statin [rosuvastatin (Crestor) 20-40 mg, atorvastatin (Lipitor) 40-80 mg] PLUS ezetimibe (Zetia) 10 mg daily for at least 3 months (*Note: that the 3 month timeframe and the addition of ezetimibe* (Zetia) are additional Company requirement for coverage eligibility and will be denied as not medically necessary\*\* if not met); OR



Policy # 00714 Original Effective Date: 12/14/2020 Current Effective Date: 01/13/2025

- ii. Patient's LDL-C is not adequately controlled [e.g., not at the LDL-C treatment goal of <70 mg/dL based on the current NLA guidelines] with a maximally tolerated stable daily statin (of any potency) PLUS ezetimibe (Zetia) 10 mg daily for at least 3 months ONLY if proof is given that a high potency maximum daily dose statin was not well tolerated (*Note that the 3 month timeframe and the addition of ezetimibe* (Zetia) are additional company requirements and will be denied as not medically necessary\*\* if not met); OR
- D. Patient has the presence of clinical atherosclerotic cardiovascular disease (either FH or non-FH); AND
  - i. Patient's LDL-C is not adequately controlled [e.g., not at the LDL-C treatment goal of <70 mg/dL based on the current NLA guidelines] due to statin intolerance; AND
  - ii. Patient must meet ALL of the following criteria for statin intolerance:
    - Patient was unable to tolerate at least 2 different statins. [The inability to tolerate one statin will be accepted if the patient experienced rhabdomyolysis or clinically-significant myonecrosis secondary to a statin. Rhabdomyolysis/myonecrosis is considered to be a muscle breakdown with signs and symptoms such as muscle pain, weakness, tenderness ALONG WITH either: a.) acute renal failure or myoglobinuria AND elevated creatine kinase levels (e.g., ≥ 10 times the upper limit of normal) OR b.) elevated creatine kinase levels (e.g., ≥ 10 times the upper limit of normal) alone]; AND
    - 2. Patient's intolerance was associated with confirmed, intolerable statin-related adverse effects [e.g., skeletal related muscle symptoms (myopathy [muscle weakness] or myalgia [muscle aches, soreness, stiffness, or tenderness])]; AND
    - 3. Patient's symptoms or biomarker changes resolved or showed significant improvement on dose decrease or discontinuation.

#### **Re-authorization**: (Patient must meet I and II)

- I. Patient previously met the initial criteria and received an approval for bempedoic acid products (Nexletol, Nexlizet); AND
- II. Patient has achieved clinically significant LDL-C lowering AND is compliant with bempedoic acid products (Nexletol, Nexlizet).
  (Note that the re-authorization criteria are additional company requirements and will be denied as not medically necessary\*\* if not met)

Policy # 00714 Original Effective Date: 12/14/2020 Current Effective Date: 01/13/2025

# When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of bempedoic acid products (Nexletol, Nexlizet) when the member has not tried and failed the required pre-requisite medications for a timeframe of at least 3 months to be **not medically necessary.**\*\*

Based on review of available data, the Company considers the use of bempedoic acid products (Nexletol, Nexlizet) when the re-authorization criteria are NOT met to be **not medically necessary.**\*\*

Based on review of available data, the Company considers the use of bempedoic acid products (Nexletol, Nexlizet) when ezetimibe (Zetia) has NOT been added to the patient's statin regimen to be **not medically necessary.**\*\*

Based on review of available data, the Company considers the use of bempedoic acid products (Nexletol, Nexlizet) for NON-familial hypercholesterolemia WITHOUT the presence of clinical atherosclerotic cardiovascular disease to be **not medically necessary.**\*\*

### When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of bempedoic acid products (Nexletol, Nexlizet) when patient selection criteria are not met (except those listed above as **not medically necessary**\*\*) to be **investigational.**\*

### **Background/Overview**

Nexletol is an adenosine triphosphate-citrate lyase (ACL) inhibitor 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. Nexlizet carries the same indication, but also contains an additional ingredient, ezetimibe, which is a cholesterol absorption inhibitor. Both products are dosed daily without regard to meals.

It should be noted that the effects of Nexletol and Nexlizet on cardiovascular morbidity and mortality have not been determined.

#### **Hypercholesterolemia/Treatment Guidelines**

Approximately 30% of the United States population has elevated LDL-C (low density lipoprotein cholesterol). There is also a subset of hypercholesterolemia, known as familial hypercholesterolemia, which can affect nearly 1 in 300 individuals. Familial hypercholesterolemia



Policy # 00714 Original Effective Date: 12/14/2020 Current Effective Date: 01/13/2025

can further be broken down into homozygous and heterozygous forms of familial hypercholesterolemia. The homozygous form is by far the rarest with an estimated incidence of 1 in 1,000,000 individuals. The gold standard for the treatment of elevated LDL-C levels is a statin given along with ezetimibe (Zetia) to provide the greatest amount of LDL-C lowering. Statin products also have proven cardiovascular outcomes.

Genetic testing is available to determine whether or not an individual has familial hypercholesterolemia, however clinical signs/symptoms are often a more practical method of diagnosing this condition. Clinical studies have used the WHO/Dutch Lipid Clinic Network Familial Hypercholesterolemia diagnostic criteria to determine if an individual had familial hypercholesterolemia. A score of >8 is representative of "definite" familial hypercholesterolemia. The criteria are located in the following chart:

	Points
Criteria	
Family history	
First-degree relative with known premature* coronary and vascular disease, OR	1
First-degree relative with known LDL-C level above the 95th percentile	
First-degree relative with tendinous xanthomata and/or arcus cornealis, OR	2
Children aged less than 18 years with LDL-C level above the 95th percentile	
Clinical history	
Patient with premature* coronary artery disease	2
Patient with premature* cerebral or peripheral vascular disease	1
Physical examination	
Tendinous xanthomata	6
Arcus cornealis prior to age 45 years	4
Cholesterol levels mg/dl (mmol/liter)	
LDL-C >= 330 mg/dL ( ≥8.5)	8
LDL-C 250 – 329 mg/dL (6.5–8.4)	5
LDL-C 190 – 249 mg/dL (5.0–6.4)	3
LDL-C 155 – 189 mg/dL (4.0–4.9)	1
DNA analysis	
Functional mutation in the LDLR, apo B or PCSK9 gene	8
Diagnosis (diagnosis is based on the total number of points obtained)	
Definite Familial Hypercholesterolemia	>8
Probable Familial Hypercholesterolemia	6-8
Possible Familial Hypercholesterolemia	3-5
Unlikely Familial Hypercholesterolemia	<3

WHO	(World	Health	<b>Organization</b> )/Dutch	Lipid	Clinic	Network	Familial
Hypercholesterolemia Criteria				_			

Premature = < 55 years in men; < 60 years in women

Policy # 00714 Original Effective Date: 12/14/2020 Current Effective Date: 01/13/2025

The 95<sup>th</sup> percentile in the "WHO/Dutch Lipid Clinic Network Familial Hypercholesterolemia Criteria" chart refers to the following LDL cholesterol values:

Men			Women				
Age (yr)	5th Percentile (LDL-C, mg/dL)	75th Percentile (LDL-C, mg/dL)	95th percentile (LDL-C, mg/dL)	Age (yr) 5th Percentile (LDL-C, mg/dL)		75th Percentile (LDL-C, mg/dL)	95th Percentile (LDL-C, mg/dL)
0–19	65	105	130	0–19	65	110	140
20-24	65	120	145	20-24	55	120	160
25-29	70	140	165	25-34	70	125	160
30–34	80	145	185	35–39	75	140	170
35–39	80	155	190	40–44	75	145	175
40-44	85	155	185	45–49	80	150	185
45–69	90	165	205	50–54	90	160	200
70 +	90	165	185	55 +	95	170	215

The above chart comes from Lipid Research Clinic Data 1983. Available at: http://www.ncbi.nlm.nih.gov/books/NBK351/table/A968/?report=objectonly

The following link for the ATP III- A distribution of LDL Cholesterol in the US Adult Populationalsoprovidespercentilevalues.Itislocatedat:http://circ.ahajournals.org/content/106/25/3237/T2.expansion.html.

The American College of Cardiology (ACC)/American Heart Association (AHA) treatment guidelines no longer set treatment goals for hyperlipidemia. The guidelines instead emphasize the appropriate intensity of statin therapy to reduce cardiovascular risk in patients who will benefit. These guidelines also emphasize the benefits of LDL-C reduction. The National Lipid Association does set LDL-C treatment goal levels for patients at various risk stratifications. Those with clinical

Policy # 00714 Original Effective Date: 12/14/2020 Current Effective Date: 01/13/2025

atherosclerotic cardiovascular disease would fall into the "very high risk" category and would therefore be treated to an LDL-C of less than 70 mg/dL. Patients with familial hypercholesterolemia could fall into either the "very high risk" or "high risk" categories, based on their patient characteristics and would therefore have a treatment goal of less than 70 mg/dL or 100 mg/dL (respectively). Risk stratification (per the National Lipid Association) is as follows:

#### **Risk Classifications:**

#### Very High Risk:

- I. Clinical ASCVD (atherosclerotic cardiovascular disease)<sup>#</sup>; OR
- II. Diabetes Mellitus with  $\geq 2$  other Major ASCVD risk factors<sup>A</sup> OR diabetes mellitus with end organ damage [e.g., increased albumin/creatinine ratio ( $\geq 30$ mg/g), chronic kidney disease, or retinopathy]

#### High Risk:

- I.  $\geq$  3 major ASCVD risk factors^; OR
- II. Diabetes Mellitus with 0-1 other Major ASCVD risk factors^; OR
- III. Chronic kidney disease (GFR  $\leq$  44 mL/min); OR
- IV. LDL-C  $\geq$  190 mg/dL (untreated); OR
- V. Quantitative risk score reaching the high risk threshold (one of the following):
  - A. ≥10% using Adult Treatment Panel III Framingham risk score for hard coronary heart disease (CHD, MI, or CHD death); OR
  - B. ≥15% using the 2013 Pooled Cohort Equations for hard ASCVD (MI, stroke, or death from CHD or stroke); OR
  - C.  $\geq$ 45% using the Framingham long-term CVD (MI, CHD death or stroke) risk calculator

#### <sup>#</sup>Clinical ASCVD (includes one of more of the following):

- I. Myocardial infarction or other acute coronary syndrome
- II. Coronary or other revascularization procedure
- III. Transient ischemic attack
- IV. Ischemic stroke
- V. Atherosclerotic peripheral arterial disease (ABI of <0.90)
- VI. Other documented atherosclerotic diseases such as
  - A. Clinically significant coronary atherosclerosis diagnosed by coronary angiography, stress test, stress echocardiography, or myocardial perfusion imaging
  - B. Renal atherosclerosis
  - C. Aortic aneurysm secondary to atherosclerosis
  - D. Carotid plaque (≥50% stenosis)

Policy # 00714 Original Effective Date: 12/14/2020 Current Effective Date: 01/13/2025

#### **^ASCVD Risk factors:**

- I. Age
  - A. Male  $\geq$  45 years
  - B. Female  $\geq$  55 years
- II. Family history of early CHD (MI, death, or coronary revascularization procedure)
  - A. <55 years of age in a male first degree relative or
  - B. <65 years of age in a female first degree relative
- III. Current cigarette smoking
- IV. High blood pressure ( $\geq 140/\geq 90 \text{ mm Hg}$ ) or on a blood pressure medication)
- V. Low HDL-C
  - A. Male <40 mg/dL
  - B. Female <50 mg/dL

#### **Treatment Goals:**

Risk	LDL-C Treatment Goal
Very High Risk	<70 mg/dL
High Risk	<100 mg/dL

#### Primary Hypercholesterolemia/Clinical Atherosclerotic Cardiovascular Disease

Given that there is no long-term cardiovascular evidence in subjects with non-familial hypercholesterolemia who do NOT have ASCVD, other proven products (e.g., statins) should be used until further evidence is provided. Note that Nexletol has cardiovascular outcomes data in patients with, or at high risk for atherosclerotic cardiovascular disease who are statin intolerant. This policy already provides coverage for these members, so no changes to coverage criteria are warranted.

Clinical ASCVD is defined as those with ACS or history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke or transient ischemic attack, or peripheral artery disease (PAD) presumed to be of atherosclerotic origin. Subclinical atherosclerosis is defined in this document as significant atherosclerotic plaque observed in an asymptomatic patient on any of the following diagnostic studies: coronary artery calcification noted on computed tomography (CT) studies, including calcium scoring, cardiac CT coronary angiography, chest CT for ruling out pulmonary embolism, chest CT for lung cancer screening, or diagnostic chest CT; carotid plaque noted on carotid ultrasound or angiography; or abnormal ankle-brachial index or plaque noted on peripheral arterial angiography. For clarity, calcium scoring alone is not indicative of ASCVD.

#### **Statin Intolerance**

Statins have been associated with muscle-related adverse effects such as myalgia (e.g., muscle aches, soreness, stiffness, or tenderness), myopathy (muscle weakness), and/or myositis (muscle inflammation). Although the incidence is variable, muscle adverse effects are reported in around 5% of patients receiving statins, but may be due to other causes (e.g., excessive exercise, other medical

Policy # 00714 Original Effective Date: 12/14/2020 Current Effective Date: 01/13/2025

conditions [hypothyroidism], non-statin medications). It is advisable to assess for drug interactions as well as to check vitamin D levels and thyroid function status. Rhabdomyolysis, which is uncommon with statin therapy, is a severe muscle-related adverse effect that results in muscle breakdown associated with muscle-related symptoms (e.g., muscle pain, weakness, tenderness) along with acute renal failure and elevated creatine kinase [CK] levels (myonecrosis). In patients with statin-related muscle adverse events, symptoms may not re-occur if the patient switches to a different statin therapy. Pravastatin and fluvastatin appear to have much less intrinsic muscle toxicity than other statins and could be considered for those who had statin related intolerable muscle symptoms.

In 2014, the NLA Statin Intolerance Panel published an update. It was stated that most statin intolerance is due to myalgia. The strongest evidence at present for statin intolerance in a population is that myalgia appears but then remits with withdrawal but reoccurs with re-challenge. The incidence of statin intolerance is widely variable. The Panel states that statins are among the safest medications available. The Panel does advise that due to statin benefits, it is safe to recommend a patient continue statin therapy even when some degree of statin intolerance is present, if the patient can reasonably tolerate the statin. A pivotal trial with Praluent called ODYSSEY ALTERNATIVE defined statin intolerance as the inability to take at least two different statins due to muscle-related adverse effects, of which one statin was administered at the lowest approved starting dose. Data also suggest that many patients who are re-challenged with statin therapy after an adverse event may be able to tolerate statin therapy long-term. Of note, in the ODYSSEY ALTERNATIVE trial with Praluent, 69.8% of patients who were considered statin intolerant were treated with atorvastatin 20 mg daily and completed the double-blind 24-week portion of the trial. This suggests that re-challenge with a statin in those purported to be statin intolerant is reasonable and may lead to successful use of a statin therapy.

# FDA or Other Governmental Regulatory Approval

#### U.S. Food and Drug Administration (FDA)

Nexletol and Nexlizet are both indicated to reduce the risk of myocardial infarction and coronary revascularization in adults who are unable to take recommended statin therapy (including those not taking a statin) with established CVD or high risk for a CVD event but without established CVD and 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 in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH).



Policy # 00714 Original Effective Date: 12/14/2020 Current Effective Date: 01/13/2025

# **Rationale/Source**

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

#### <u>Nexletol</u>

#### **Primary** Hyperlipidemia Trials in Adults

The efficacy of Nexletol was investigated in two multicenter, randomized, double-blind, placebocontrolled trials that enrolled 3,009 adult patients with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who were on maximally tolerated statin therapy. Demographics and baseline disease characteristics were balanced between the treatment arms in all trials. In both trials, the maximum LDL-C lowering effects occurred at Week 4.

Study 1 was a multicenter, randomized, double-blind, placebo-controlled 52-week trial that evaluated safety and efficacy of bempedoic acid in patients with HeFH and/or ASCVD. Efficacy of Nexletol was evaluated at Week 12. The trial included 2,230 patients randomized 2:1 to receive either Nexletol (n = 1488) or placebo (n = 742) as add-on to a maximally tolerated lipid lowering therapy. Maximally tolerated lipid lowering therapy was defined as a maximally tolerated statin dose alone or in combination with other lipid-lowering therapies. Patients were stratified by presence of HeFH and by baseline statin intensity. Patients on simvastatin 40 mg per day or higher and patients taking PCSK9 inhibitors were excluded from the trial.

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).

Study 2 was a multi-center, randomized, double-blind, placebo-controlled, 52-week trial in patients with HeFH and/or ASCVD. Efficacy of Nexletol was evaluated at Week 12. The trial included 779 patients randomized 2:1 to receive either Nexletol (n = 522) or placebo (n = 257) as add-on to a maximally tolerated lipid lowering therapy. Maximally tolerated lipid lowering therapy was defined as a maximally tolerated statin dose alone or in combination with other lipid-lowering therapies. Patients were stratified by presence of HeFH and baseline statin intensity. Patients on simvastatin 40 mg/day or higher were excluded from the trial.

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).

Policy # 00714 Original Effective Date: 12/14/2020 Current Effective Date: 01/13/2025

#### Cardiovascular Outcomes Trial in Adults with CVD or at High Risk for CVD

Trial 3 was a randomized, double-blind, placebo-controlled, event-driven trial in 13,970 adult patients with established CVD (70%) or at high risk for a CVD event but without CVD (30%) who were not receiving recommended statin dosages. Patients with established CVD had documented history of coronary artery disease, symptomatic peripheral arterial disease, and/or cerebrovascular atherosclerotic disease. Patients without established CVD were considered at high risk for CVD based on meeting at least one of the following criteria:

- Diabetes mellitus (type 1 or type 2) in females over 65 years of age or males over 60 years of age;
- A Reynolds Risk score > 30% or a SCORE Risk score > 7.5% over 10 years. Reynolds risk score and SCORE risk score evaluate a 10-year risk of having a cardiovascular (CV) event. The Reynolds risk score is based on the following risk factors: sex, age, smoking status, systolic blood pressure, total cholesterol, HDL cholesterol, high sensitivity C-reactive protein (hsCRP), and familial history of CVD events. LDL-C is an additional risk factor considered in SCORE risk score; OR
- A coronary artery calcium score > 400 Agatston units at any time in the past.

Patients were randomized 1:1 to receive either oral Nexletol 180 mg per day (n = 6,992) or placebo (n = 6,978), alone or as an add on to other background lipid-lowering therapies. Background therapy could include less than low-intensity statin dosages.

The risk for the primary composite endpoint (MACE-4: time to first occurrence of CV death, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization; p=0.0037) and the key secondary composite endpoint (MACE-3: time to first occurrence of CV death, nonfatal myocardial infarction, or nonfatal stroke; p=0.0058) was significantly reduced in Nexletol treated patients compared to placebo-treated patients. The difference between the Nexletol and placebo groups in mean percent change in LDL-C from baseline to Month 6 was -20% (95% CI: -21%, -19%).

#### <u>Nexlizet</u>

The efficacy of Nexlizet was investigated in a single, multi-center, randomized, double-blind, placebo-controlled, parallel group trial that enrolled 301 patients with heterozygous familial hypercholesterolemia, established atherosclerotic cardiovascular disease, or multiple risk factors for cardiovascular disease on maximally tolerated statin therapy. The efficacy of Nexlizet in patients with multiple risk factors for cardiovascular disease has not been established.

Study 1 randomized patients 2:2:2:1 to receive either Nexlizet (180 mg of bempedoic acid and 10 mg of ezetimibe) (n = 86), bempedoic acid 180 mg (n = 88), ezetimibe 10 mg (n = 86), or placebo

Policy # 00714 Original Effective Date: 12/14/2020 Current Effective Date: 01/13/2025

(n = 41) once daily as add-on to maximally tolerated statin therapy. Patients were stratified by cardiovascular risk and baseline statin intensity. Patients on simvastatin 40 mg per day or higher and patients taking non-statin lipid-lowering therapy (including fibrates, niacin, bile acid sequestrants, ezetimibe, and PCSK9 inhibitors) were excluded from the trial.

The primary efficacy outcome measure of the study was the percent change from baseline to Week 12 in LDL-C. The difference between Nexlizet and placebo in mean percent change in LDL-C from baseline to Week 12 was -38% (95% CI: -47%, -30%; 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 Nexlizet and placebo in mean percent change from baseline to Week 12 was -5% for HDL and median percent change from baseline to Week 12 was -11% for TG. The maximum LDL-C lowering effect was observed at Week 4.

### **References**

- 1. Nexletol [package insert]. Esperion Therapeutics, Inc. Ann Arbor, Michigan. March 2024.
- 2. Nexlizet [package insert]. Esperion Therapeutics, Inc. Ann Arbor, Michigan. March 2024.
- Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. Circulation. 2014;129(25 Suppl 2):S1-S45. Available at http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a.
- Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patientcentered management of dyslipidemia: Part 1-executive summary. J Clin Lipidol. 2014;8:473-488. Available at: http://www.lipidjournal.com/article/S1933-2874(14)00274-8/pdf.
- 5. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patientcentered management of dyslipidemia: Part 1-full report. J Clin Lipidol. 2015;9:129-169.
- 6. Rosenson RS, Baker SK, Jacobson TA, et al. An assessment by the statin muscle safety task force: 2014 update. J Clin Lipidol. 2014;8:S58-S71.
- 7. Guyton JR, Bays HE, Grundy SM, Jacobson TA. An assessment by the Statin Intolerance Panel: 2014 update. J Clin Lipidol. 2014;8:S72-S81.
- 8. Moriarty PM, Jacobson TA, Bruckert E, et al. Efficacy and safety of alirocumab, a monoclonal antibody to PCSK9, in statin-intolerant patients: design and rationale of ODYSSEY ALTERNATIVE, a randomized phase 3 trial. J Clin Lipidol. 2014;8:554-561.
- 9. Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of statins in routine care settings. Ann Intern Med. 2013;158(7):526-534.
- 10. Mampuya WM, Frid D, Rocco M, et al. Treatment strategies in patients with statin intolerance: the Cleveland Clinic Experience. Am Heart J. 2013;166(3):597-603.
- 11. 95th Percentile Chart: Chapter 31: Cholesterol, Triglycerides, and Associated Lipoproteins; In Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition. Walker HK, Hall WD, Hurst JW, et al. Available at: http://www.ncbi.nlm.nih.gov/books/NBK351/table/A968/?report=objectonly.



Policy # 00714 Original Effective Date: 12/14/2020 Current Effective Date: 01/13/2025

- 12. Alternative percentile link: ATP III Final Report Appendix III-A Distributions of Total Cholesterol, LDL Cholesterol, HDL Cholesterol, and Triglycerides in the U.S. Adult Population, NHANES III Data (1988-1994. Available at: http://circ.ahajournals.org/content/106/25/3237/T2.expansion.html.
- 13. Steg G, Schwartz GG, Szarek M, et al, on behalf of the ODYSSEY Outcomes Investigators and Committees. The ODYSSEY Outcomes trial: topline results. Alirocumab in patients after acute coronary syndrome. Presented at: the American College of Cardiology 67<sup>th</sup> Scientific Sessions; Orlando, FL; March 10-12, 2018. Presented March 10, 2018. Available at: <u>http://www.acc.org/educationand-meetings/image-and-slide-gallery/media-</u> detail?id=90e30055844c402ba16d54fb05e45136.
- Nissen SE, Lincoff AM, Brennan D, Ray KK, Mason D, Kastelein JJP, Thompson PD, Libby P, Cho L, Plutzky J, Bays HE, Moriarty PM, Menon V, Grobbee DE, Louie MJ, Chen CF, Li N, Bloedon L, Robinson P, Horner M, Sasiela WJ, McCluskey J, Davey D, Fajardo-Campos P, Petrovic P, Fedacko J, Zmuda W, Lukyanov Y, Nicholls SJ; CLEAR Outcomes Investigators. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. N Engl J Med. 2023 Apr 13;388(15):1353-1364. doi: 10.1056/NEJMoa2215024. Epub 2023 Mar 4. PMID: 36876740.

### **Policy History**

Original Effectiv	ve Date: 12/14/2020				
Current Effectiv	ve Date: 01/13/2025				
11/05/2020	Medical Policy Committee review				
11/11/2020	Medical Policy Implementation Committee approval. New policy.				
11/04/2021	Medical Policy Committee review				
11/10/2021	Medical Policy Implementation Committee approval. No change to coverage.				
11/03/2022	Medical Policy Committee review				
11/09/2022 Medical Policy Implementation Committee approval. No change to coverage.					
11/02/2023	Medical Policy Committee review				
11/08/2023	Medical Policy Implementation Committee approval. Coverage eligibility				
	unchanged.				
12/05/2024	Medical Policy Committee review				
12/11/2024	Medical Policy Implementation Committee approval. Updated policy to reflect new				
	FDA labeled indication, to reduce the risk of MI and coronary revascularization in				
	adults who are unable to take recommended statin therapy in patients who have				
established CVD or are at high risk for a CVD event, but do not hav					
	CVD. Updated policy to reflect updated FDA labeled indication, to reduce LDL-C				
	in adults with primary hyperlipidemia. Added the use of Nexlizet/Nexletol for				
	NON-familial hypercholesterolemia WITHOUT the presence of clinical				
	atherosclerotic cardiovascular disease as not medically necessary.				

Next Scheduled Review Date: 12/2025

Policy # 00714 Original Effective Date: 12/14/2020 Current Effective Date: 01/13/2025

\*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
  - 1. Consultation with technology evaluation center(s);
  - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
  - 3. Reference to federal regulations.

\*\*Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

**NOTICE:** If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.



Policy # 00714 Original Effective Date: 12/14/2020 Current Effective Date: 01/13/2025

**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

**NOTICE:** Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

