



Louisiana

Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) Inhibitors [alirocumab (Praluent[®]), evolocumab (Repatha[™])]

Policy # 00472

Original Effective Date: 12/16/2015

Current Effective Date: 07/13/2020

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 proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors [alirocumab (Praluent[®])[†], evolocumab (Repatha[™])[‡]] to be **eligible for coverage**.**

evolocumab (Repatha)

Patient Selection Criteria

Based on review of available data, the Company may consider the use of evolocumab (Repatha) when the following criteria are met:

Initial Authorization: (Patient must meet I, II, III, IV, and V)

- I. Patient is 18 years of age or older (EXCEPT in familial hypercholesterolemia (FH) where age can be 13 years of age or older); AND
- II. Patient is compliant with any medications required for therapy prior to receiving authorization for evolocumab (Repatha); AND
- III. evolocumab (Repatha) will NOT be used in combination with lomitapide (Juxtapid[®])[‡] or mipomersen (Kynamro[®])[‡]; AND
- IV. evolocumab (Repatha) will be used along with a maximally tolerated statin [in those who are not considered statin intolerant (see below for statin intolerance)]; AND

(Note that this criterion is an additional company requirement for evolocumab [Repatha] for members with atherosclerotic cardiovascular disease and will be denied as not

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*medically necessary** if not met. For other indications, this will be denied as investigational* if not met.)*

V. Patient must meet one of the following (A, B, C, or D):

A. Patient has a diagnosis of FH (withOUT 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 potency maximum daily dose statin [rosuvastatin (Crestor[®])[‡] 40 mg, atorvastatin (Lipitor[®])[‡] 80 mg] for at least 3 months (*Note that the 3 month timeframe is an additional company requirement and will be denied as not medically necessary** if not met*); OR
- 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) 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 is an additional company requirement and will be denied as not medically necessary** if not met*); OR

B. Patient has a diagnosis of FH (withOUT 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:
 1. 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

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- 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 atherosclerotic cardiovascular disease (either FH or non-FH); AND
- [Note that all criteria listed under criteria "C" for evolocumab (Repatha) are additional company requirements and will be denied as not medically necessary** if not met.]*
- 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 potency maximum daily dose statin [rosuvastatin (Crestor) 40 mg, atorvastatin (Lipitor) 80 mg] for at least 3 months; OR
 - 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) for at least 3 months ONLY if proof is given that a high potency maximum daily dose statin was not well tolerated; OR
- D. Patient has the presence of atherosclerotic cardiovascular disease (either FH or non-FH); AND
- [Note that all criteria listed under criteria "D" for evolocumab (Repatha) are additional company requirements and will be denied as not medically necessary** if not met.]*

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- 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:
 1. 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 evolocumab (Repatha); AND
- II. Patient has achieved clinically significant LDL-C lowering AND is compliant with evolocumab (Repatha).

*(Note that the re-authorization criteria are additional company requirements and will be denied as not medically necessary** if not met)*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of evolocumab (Repatha) when the criteria for coverage are not met for patients with atherosclerotic cardiovascular disease (e.g., LDL-C goal, statin therapy, timeframes, etc.) to be **not medically necessary**.**

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Based on review of available data, the Company considers the use of evolocumab (Repatha) in those with familial hypercholesterolemia (without atherosclerotic cardiovascular disease) when the member has not tried 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 evolocumab (Repatha) 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 evolocumab (Repatha) for NON-familial hypercholesterolemia withOUT the presence of 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 evolocumab (Repatha) when patient selection criteria are not met (except those listed above as **not medically necessary*****) to be **investigational**.*

alirocumab (Praluent)

Patient Selection Criteria

Based on review of available data, the Company may consider the use of alirocumab (Praluent) when the following criteria are met:

Initial Authorization: (Patient must meet I, II, III, IV, and V)

- 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 alirocumab (Praluent); AND
- III. alirocumab (Praluent) will NOT be used in combination with lomitapide (Juxtapid) or mipomersen (Kynamro); AND

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- IV. alirocumab (Praluent) will be used along with a maximally tolerated statin [in those who are not considered statin intolerant (see below for statin intolerance)]; AND
*(Note that this criterion is an additional company requirement for alirocumab [Praluent] for members with atherosclerotic cardiovascular disease and will be denied as not medically necessary** if not met. For other indications, this will be denied as investigational* if not met.)*
- V. Patient must meet one of the following (A, B, C, or D):
- A. Patient has a diagnosis of FH (withOUT 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] with a high potency maximum daily dose statin [rosuvastatin (Crestor) 40mg, atorvastatin (Lipitor) 80mg] for at least 3 months *(Note that the 3 month timeframe is an additional company requirement and will be denied as not medically necessary** if not met)*; OR
 - 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) 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 is an additional company requirement and will be denied as not medically necessary** if not met)*; OR
- B. Patient has a diagnosis of FH (withOUT 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:

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1. 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 atherosclerotic cardiovascular disease (either FH or non-FH); AND
- [Note that all criteria listed under criteria "C" for alirocumab (Praluent) are additional company requirements and will be denied as not medically necessary** if not met.]*
- 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 potency maximum daily dose statin [rosuvastatin (Crestor) 40mg, atorvastatin (Lipitor) 80mg] for at least 3 months; OR
 - 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) for at least 3 months ONLY if proof is given that a high potency maximum daily dose statin was not well tolerated; OR
- D. Patient has the presence of atherosclerotic cardiovascular disease (either FH or non-FH); AND

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[Note that all criteria listed under criteria “D” for alirocumab (Praluent) are additional company requirements and will be denied as not medically necessary if not met.]

- 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:
 1. 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 alirocumab (Praluent); AND
- II. Patient has achieved clinically significant LDL-C lowering AND is compliant with alirocumab (Praluent).

*(Note that the re-authorization criteria are additional company requirements and will be denied as not medically necessary** if not met)*

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When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of alirocumab (Praluent) when the criteria for coverage are not met for patients with atherosclerotic cardiovascular disease (e.g., LDL-C goal, statin therapy, timeframes, etc) to be **not medically necessary.****

Based on review of available data, the Company considers the use of alirocumab (Praluent) in those with familial hypercholesterolemia (without atherosclerotic cardiovascular disease) when the member has not tried 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 alirocumab (Praluent) 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 alirocumab (Praluent) for NON-familial hypercholesterolemia withOUT the presence of 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 alirocumab (Praluent) when patient selection criteria are not met (except those listed above as **not medically necessary****) to be **investigational.***

Background/Overview

Praluent and Repatha belong to a new class of medications known as the PCSK9 inhibitors. Each of these products is a human monoclonal antibody that binds to PCSK9. PCSK9 binds to the low density lipoprotein receptors (LDLR) on the surface of hepatocytes to promote LDLR degradation within the liver. LDLR is the primary receptor that clears LDL-C. By inhibiting the binding of

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PCSK9 to the LDLR, the PCSK9 inhibitors increase the number of LDLRs available to clear LDL-C, thereby lowering LDL-C levels.

Praluent is indicated as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for the treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) to reduce LDL-C. Praluent is also indicated to reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease. The recommended starting dose of Praluent is 75 mg administered subcutaneously once every 2 weeks, since most patients achieve adequate LDL-C reduction with this dose. If adequate LDL-C lowering is not reached, the Praluent dose can be increased to a maximum dose of 150 mg subcutaneously every 2 weeks. An alternative for those who prefer less frequent dosing is 300 mg once every 4 weeks.

Repatha is indicated to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease, as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) to reduce LDL-C, and as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C. The recommended dose of Repatha for those with non-HoFH type hypercholesterolemia is 140 mg administered subcutaneously every 2 weeks or 420 mg administered subcutaneously once monthly. For those with homozygous familial hypercholesterolemia, the recommended dose is 420 mg subcutaneously once monthly.

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 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.

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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. The clinical studies for the PCSK9 inhibitors 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:

WHO (World Health Organization)/Dutch Lipid Clinic Network Familial Hypercholesterolemia Criteria

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	Points
Criteria	
Family history	
First-degree relative with known premature* coronary and vascular disease, OR First-degree relative with known LDL-C level above the 95th percentile	1
First-degree relative with tendinous xanthomata and/or arcus cornealis, OR Children aged less than 18 years with LDL-C level above the 95th percentile	2
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 \geq 330 mg/dL (\geq 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 <i>LDLR</i> , <i>apo B</i> or <i>PCSK9</i> 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

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

The 95th percentile in the “WHO/Dutch Lipid Clinic Network Familial Hypercholesterolemia Criteria” chart refers to the following LDL cholesterol values:

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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>

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The following link for the ATP III- A distribution of LDL Cholesterol in the US Adult Population also provides percentile values. It is located at: <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 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. ASCVD (atherosclerotic cardiovascular disease)[#]; OR
- II. Diabetes Mellitus with ≥ 2 other Major ASCVD risk factors[^] OR diabetes mellitus with end organ damage [e.g., increased albumin/creatinine ratio (≥ 30 mg/g), chronic kidney disease, or retinopathy]

High Risk:

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

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Louisiana

Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) Inhibitors [alirocumab (Praluent[®]), evolocumab (Repatha[™])]

Policy # 00472

Original Effective Date: 12/16/2015

Current Effective Date: 07/13/2020

C. $\geq 45\%$ using the Framingham long-term CVD (MI, CHD death or stroke) risk calculator

#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. Coronary atherosclerosis
 - B. Renal atherosclerosis
 - C. Aortic aneurysm secondary to atherosclerosis
 - D. Carotid plaque ($\geq 50\%$ stenosis)

^ASCVD Risk factors:

- I. Age
 - A. Male ≥ 45 years
 - B. Female ≥ 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 ($\geq 140/\geq 90$ 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

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Primary Hypercholesterolemia/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 both PCSK9 products have cardiovascular outcomes data in patients with atherosclerotic cardiovascular disease who have LDL-C \geq 70 mg/dL despite therapy. This policy already provides coverage for these members, so no changes in coverage criteria are warranted.

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 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

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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)

Praluent was approved in July of 2015 as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C. This label has since changed.

In April 2019, Praluent's label changed to the following: indicated as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for the treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) to reduce LDL-C as well as to reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease.

Repatha was approved in August of 2015 as an adjunct to diet and maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease who require additional lowering of LDL-C. Repatha is also indicated as an adjunct to diet and other LDL-C lowering therapies (statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia who require additional lowering of LDL-C. This label has since changed.

In late 2017, Repatha was relabeled to the following: to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease, as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) to reduce LDL-C, and as an adjunct to diet and other LDL-lowering therapies

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(e.g., statins, ezetimibe, LDL apheresis) in patients with HoFH who require additional lowering of LDL-C.

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, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Praluent Studies

Praluent was studied in patients with primary hyperlipidemia (with clinical atherosclerotic cardiovascular disease) and patients with heterozygous familial hypercholesterolemia.

Study 1 was a multicenter, double-blind, placebo-controlled trial that randomly assigned 1,553 patients to Praluent 150 mg every 2 weeks and 788 patients to placebo. All patients were taking maximally tolerated statin doses with or without other lipid modifying therapy, and required additional LDL-C reduction. At week 24, the treatment difference between Praluent and placebo in mean LDL-C percent change was -58% (95% CI: -61%, -56%; $p < 0.0001$).

Study 2 was a multicenter, double blind, placebo-controlled trial that randomly assigned 209 patients to Praluent and 107 patients to placebo. All patients were taking maximally tolerated statin doses with or without other lipid modifying therapy, and required additional LDL-C reduction. At week 12, the mean percent change from baseline in LDL-C was -45% with Praluent compared to 1% with placebo, and the treatment difference between Praluent 75 mg every 2 weeks and placebo in mean LDL-C percent change was -46% (95% CI: -53%, -39%). At week 12, if additional lowering of LDL-C was needed, Praluent was up-titrated to 150 mg every 2 weeks for the remainder of the trial. At week 24, the mean percent change from baseline in LDL-C was -44% with Praluent and -2% with placebo, and the treatment difference between Praluent and placebo in mean LDL-C percent change was -43% (95% CI: -50%, -35; $p < 0.0001$). The dose was up-titrated to 150 mg every 2 weeks in 17% of patients treated with Praluent.

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Studies 3 and 4 were randomized, multicenter, placebo-controlled trials that included 490 patients assigned to Praluent and 245 patients assigned to placebo. All patients in the trial had HeFH, and were taking maximally tolerated statin doses with or without other lipid modifying therapy, and required additional LDL-C reduction. At week 12, the treatment difference between Praluent 75 mg every 2 weeks and placebo in mean LDL-C percent change was -48% (95% CI: -52%, -44%). At week 12, if additional lowering of LDL-C was needed, Praluent was up-titrated to 150 mg every 2 weeks for the remainder of the trial. At week 24, the mean treatment difference between Praluent and placebo in mean LDL-C percent change from baseline was -54% (95% CI: -59%, -50%; $p < 0.0001$). The dose was up-titrated to 150 mg every 2 weeks in 42% of patients treated with Praluent.

Study 5 was a multicenter, double-blind, placebo-controlled trial that randomly assigned 72 patients to Praluent 150 mg every 2 weeks and 35 patients to placebo. All patients were taking maximally tolerated statin doses with or without other lipid modifying therapy, and required additional LDL-C reduction. At week 24, the treatment difference between Praluent and placebo in mean LDL-C percent change was -36% (95% CI: -49%, -24%; $p < 0.0001$).

Study 6 was a multicenter, double-blind, placebo-controlled trial in 18,924 adult patients followed for up to 5 years. Patients had an acute coronary syndrome event 4 to 52 weeks prior to randomization and were treated with a lipid-modifying therapy (LMT) regimen that was statin-intensive (defined as atorvastatin 40 or 80 mg, or rosuvastatin 20 or 40 mg) or at a maximally tolerated dose of a statin, with or without other LMT. Patients were randomized to receive either Praluent 75 mg once every two weeks or placebo once every two weeks. At month 2, if additional LDL-C lowering was required based on pre-specified LDL-C criteria ($LDL-C \geq 50$ mg/dL), Praluent was adjusted to 150 mg every two weeks. Most patients (89%) were receiving statin-intensive therapy with or without other LMT at randomization. The mean LDL-C value at baseline was 92.4 mg/dL. Praluent significantly reduced the risk for the primary composite endpoint (time to first occurrence of coronary heart disease death, non-fatal myocardial infarction, fatal and non-fatal ischemic stroke, or unstable angina requiring hospitalization: $p = 0.0003$).

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Repatha Studies

Repatha was studied in patients with primary hyperlipidemia (with clinical atherosclerotic cardiovascular disease), patients with heterozygous familial hypercholesterolemia, and patients with homozygous familial hypercholesterolemia.

Study 1 was a multicenter, double-blind, randomized controlled trial in which patients were initially randomized to an open-label specific statin regimen for a 4-week lipid stabilization period followed by random assignment to subcutaneous injections of Repatha 140 mg every 2 weeks, Repatha 420 mg once monthly, or placebo for 12 weeks. The trial included 296 patients with atherosclerotic cardiovascular disease who received Repatha or placebo as add-on therapy to daily doses of atorvastatin 80 mg, rosuvastatin 40 mg, or simvastatin 40 mg. In these patients with atherosclerotic cardiovascular disease who were on maximum-dose statin therapy, the difference between Repatha and placebo in mean percent change in LDL-C from baseline to week 12 was -71% (95% CI: -81%, -61%; $p < 0.0001$) and -63% (95% CI: -76%, -50%; $p < 0.0001$) for the 140 mg every 2 weeks and 420 mg once monthly dosages, respectively.

Study 2 was a multicenter, double-blind, randomized, placebo-controlled, 52-week trial that included 139 patients with atherosclerotic cardiovascular disease who received protocol-determined background lipid-lowering therapy of atorvastatin 80 mg daily with or without ezetimibe 10 mg daily. After stabilization on background therapy, patients were randomly assigned to the addition of placebo or Repatha 420 mg administered subcutaneously once monthly. In these patients with atherosclerotic cardiovascular disease on maximum-dose atorvastatin therapy with or without ezetimibe, the difference between Repatha 420 mg once monthly and placebo in mean percent change in LDL-C from baseline to week 52 was -54 % (95% CI: -65%, -42%; $p < 0.0001$).

Study 3 was a multicenter, double-blind, randomized, placebo-controlled, 12-week trial in 329 patients with heterozygous familial hypercholesterolemia on statins with or without other lipid-lowering therapies. Patients were randomized to receive subcutaneous injections of Repatha 140 mg every two weeks, 420 mg once monthly, or placebo. HeFH was diagnosed by the Simon Broome criteria. In these patients with HeFH on statins with or without other lipid lowering therapies, the differences between Repatha and placebo in mean percent change in LDL-C from baseline to week 12 was -61% (95% CI: -67%, -55%; $p < 0.0001$) and -60% (95% CI: -68%, -52%; $p < 0.0001$) for the 140 mg every 2 weeks and 420 mg once monthly dosages, respectively.

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Study 4 was a multicenter, double-blind, randomized, placebo-controlled, 12-week trial in 49 patients (not on lipid-apheresis therapy) with homozygous familial hypercholesterolemia (HoFH). In this trial, 33 patients received subcutaneous injections of 420 mg of Repatha once monthly and 16 patients received placebo as an adjunct to other lipid-lowering therapies (e.g., statins, ezetimibe). The diagnosis of HoFH was made by genetic confirmation or a clinical diagnosis based on a history of an untreated LDL-C concentration > 500 mg/dL together with either xanthoma before 10 years of age or evidence of HeFH in both parents. In these patients with HoFH, the difference between Repatha and placebo in mean percent change in LDL-C from baseline to week 12 was -31% (95% CI: -44%, -18%; $p < 0.0001$). Patients known to have two LDL-receptor negative alleles (little to no residual function) did not respond to Repatha.

Study 5 was a 12-week trial in subjects with primary hyperlipidemia who were assigned to Repatha 140 mg every 2 weeks, Repatha 420 mg once monthly, or placebo for 12 weeks. The trial included subjects who received Repatha, placebo, or Zetia as add on therapy to a statin. The difference between Repatha and placebo in mean percent change in LDL-C from baseline to week 12 was -71% and -63% for the 140 mg every 2 weeks dose and the 420 mg once monthly dosages, respectively. The difference between Repatha and Zetia in LDL-C change from baseline to week 12 was -45% and -41% for the twice monthly, and once monthly dosages, respectively.

Study 6 was a double-blind, randomized, placebo-controlled, event driven trial in 27,564 adult patients with established cardiovascular disease and with LDL-C ≥ 70 mg/dL and/or non-HDL-C ≥ 100 mg/dL despite high or moderate-intensity statin therapy. Patients were randomly assigned 1:1 to receive either subcutaneous injections of Repatha (140 mg every 2 weeks or 420 mg once monthly) or placebo. Most patients were on a high (69%) or moderate-intensity (30%) statin therapy at baseline, and 5% were also taking ezetimibe. On stable background lipid-lowering therapy, the median LDL-C at baseline was 92 mg/dL; the mean (SD) was 98 (28) mg/dL. Repatha significantly reduced the risk for the primary composite endpoint (time to first occurrence of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization; $p < 0.0001$) and the key secondary composite endpoint (time to first occurrence of cardiovascular death, myocardial infarction, or stroke; $p < 0.0001$).

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- 12/03/2015 Medical Policy Committee review
- 12/16/2015 Medical Policy Implementation Committee approval. New Policy
- 12/01/2016 Medical Policy Committee review
- 12/21/2016 Medical Policy Implementation Committee approval. No change to coverage.
- 03/02/2017 Medical Policy Committee review
- 03/15/2017 Medical Policy Implementation Committee approval. Removed section regarding Homozygous Familial Hypercholesterolemia. Made a separate section for the re-authorization criteria (criteria already existed).
- 05/03/2018 Medical Policy Committee review

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- 05/16/2018 Medical Policy Implementation Committee approval. Updated with new Repatha indication and subsequent denial reason. Updated denial reason for non-concomitant use of a statin. Updated background information and rationale.
- 06/07/2018 Medical Policy Committee review
- 06/20/2018 Medical Policy Implementation Committee approval. Removed the requirement for Zetia usage.
- 06/06/2019 Medical Policy Committee review
- 06/19/2019 Medical Policy Implementation Committee approval. Updated with new Praluent indication and subsequent denial reason. Updated denial reason for non-concomitant use of a statin. Updated background information and rationale.
- 06/04/2020 Medical Policy Committee review
- 06/10/2020 Medical Policy Implementation Committee approval. No change to coverage.
- Next Scheduled Review Date: 06/2021

*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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated 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.

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****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.

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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.

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.

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