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

Policy # 00472
Original Effective Date: 12/16/2015
Current Effective Date: 09/09/2024

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**** when the patient selection criteria are met for the requested drug.

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 10 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®)‡, bempedoic acid (Nexletol®)‡, bempedoic acid/ezetimibe (Nexlizet®)‡, 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 specific patient selection criterion is an additional company requirement for evolocumab [Repatha] for members with clinical 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 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®)‡ 20-40 mg, atorvastatin (Lipitor®)‡ 40-80 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-intensity 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 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:
    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 clinical 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-intensity statin [rosuvastatin (Crestor) 20-40 mg, atorvastatin (Lipitor) 40-80 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-intensity statin was not well tolerated; OR

D. Patient has the presence of clinical 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.]*
   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)*

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

Policy # 00472
Original Effective Date: 12/16/2015
Current Effective Date: 09/09/2024

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 clinical 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 evolocumab (Repatha) in those with familial hypercholesterolemia (without clinical 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 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 evolocumab (Repatha) when patient selection criteria are NOT met (except those listed above as **not medically necessary****) to be **investigational.***

evolocumab (Repatha) 420 mg Every Two Weeks Dosing Override

Patient Selection Criteria
Based on review of available data, the Company may consider the use of evolocumab (Repatha) 420 mg every 2 weeks when the following criteria are met, in addition to, the evolocumab (Repatha) criteria in the above section:

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

Policy # 00472
Original Effective Date: 12/16/2015
Current Effective Date: 09/09/2024

Initial Authorization: (Patient must meet I and II)

I. Patient meets ONE of the following (A, B, or C):
   A. Patient has had genetic confirmation of two mutant alleles at the low-density lipoprotein receptor (LDLR), apolipoprotein B (apo B), proprotein convertase subtilisin kexin type 9 (PCSK9) or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene locus; OR
   B. Patient has an untreated LDL-C level > 500 mg/dL AND meets ONE of the following (i or ii):
      (Note: Untreated refers to prior to therapy with any antihyperlipidemic agent.)
      i. Patient had clinical manifestations of homozygous familial hypercholesterolemia (HoFH) before the age of 10 years; OR
      (Note: Clinical manifestations of HoFH are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas, or xanthelasma.)
      ii. Both parents of the patient had untreated LDL-C levels or total cholesterol levels consistent with heterozygous familial hypercholesterolemia (HeFH); OR
      (Note: An example of HeFH in both parents would be if both had an untreated LDL-C level ≥ 190 mg/dL and/or an untreated total cholesterol level > 250 mg/dL)
   C. Patient has a treated LDL-C level ≥ 300 mg/dL AND meets ONE of the following (i or ii):
      (Note: Treated refers to after therapy with at least one antihyperlipidemic agent.)
      i. Patient had clinical manifestations of HoFH before the age of 10 years; OR
      (Note: Examples of clinical manifestations of HoFH are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma.)
      ii. Both parents of the patient had untreated LDL-C levels or total cholesterol levels consistent with HeFH; AND
      (Note: An example of HeFH in both parents would be if both had an untreated LDL-C ≥ 190 mg/dL and/or an untreated total cholesterol > 250 mg/dL.)

II. Patient's LDL-C is not adequately controlled (e.g., not at the patient's LDL-C treatment goal based on the current NLA guidelines and patient characteristics) after a 12 week trial of evolocumab (Repatha) 420 mg once monthly dosing. An exception to this criterion will be patients undergoing lipid apheresis.

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

I. Patient previously met the initial criteria and received an approval for evolocumab (Repatha) 420 mg every 2 weeks dosing; AND
II. Patient has achieved clinically significant LDL-C lowering AND is compliant with evolocumab (Repatha) 420 mg every 2 weeks dosing.
*(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) 420 mg every 2 weeks dosing when the re-authorization criteria are NOT met 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) 420 mg every 2 weeks dosing when patient selection criteria are NOT met (EXCEPT the re-authorization criteria 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:

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

Policy # 00472
Original Effective Date: 12/16/2015
Current Effective Date: 09/09/2024

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

I. Patient is 18 years of age or older (EXCEPT in HeFH where age can be 8 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) bempedoic acid (Nexletol), bempedoic acid/ezetimibe (Nexlizet), or mipomersen (Kynamro); AND

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 specific patient selection criterion is an additional company requirement for alirocumab [Praluent] for members with clinical *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 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] with a high-intensity statin [rosuvastatin (Crestor) 20-40mg, atorvastatin (Lipitor) 40-80mg] 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-intensity 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 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:
      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 clinical 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-intensity statin [rosuvastatin (Crestor) 20-40mg, atorvastatin (Lipitor) 40-80mg] 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-intensity statin was not well tolerated; OR

D. Patient has the presence of clinical atherosclerotic cardiovascular disease (either FH or non-FH); AND
[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; AND

VI. There is clinical evidence or patient history that suggests the use of evolocumab (Repatha) will be ineffective or cause an adverse reaction to the patient.
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*

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

Policy # 00472
Original Effective Date: 12/16/2015
Current Effective Date: 09/09/2024

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

I. Patient previously met the initial criteria [including reasoning for the inability to use evolocumab (Repatha)] 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)*

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 clinical 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 clinical 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 clinical atherosclerotic cardiovascular disease to be **not medically necessary.****

Based on review of available data, the Company considers the use of alirocumab (Praluent) when there is no clinical evidence or patient history that suggests the use of evolocumab (Repatha) will be ineffective or cause an adverse reaction to the patient to be **not medically necessary.****

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

Policy # 00472
Original Effective Date: 12/16/2015
Current Effective Date: 09/09/2024

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 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, to reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease, as an adjunct to other LDL-C lowering therapies in adult patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C, and as an adjunct to diet and other LDL-C lowering therapies in pediatric patients aged 8 years and older with HeFH to reduce LDL-C. The recommended dose of Praluent is 75 mg administered subcutaneously once every 2 weeks, 150 mg administered subcutaneously once every 2 weeks, or 300 mg administered subcutaneously once every 4 weeks, depending on the indication. In pediatric patients, the recommended dosing of Praluent is 150 mg administered subcutaneously once every 4 weeks or 300 mg administered subcutaneously once every 4 weeks depending on the patient's weight. Dosing may be adjusted for pediatric patients if the LDL-C response in inadequate. See the package insert for complete dosing recommendations.

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

Policy # 00472
Original Effective Date: 12/16/2015
Current Effective Date: 09/09/2024

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, as an adjunct to diet and other LDL-C lowering therapies in pediatric patients aged 10 years and older with 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 adults and pediatric patients aged 10 years and older 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, however the dosage can be increased to 420 mg subcutaneously once every 2 weeks if a clinically meaningful response is not achieved in 12 weeks with the 420 mg once monthly dosing. Patients with HoFH undergoing lipid apheresis may initiate treatment with 420 mg subcutaneously every 2 weeks to correspond with their apheresis schedule.

It should be noted that there are no studies that have demonstrated superiority of one PCSK-9 inhibitor over the other.

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.

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

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

Policy # 00472
Original Effective Date: 12/16/2015
Current Effective Date: 09/09/2024

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

	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 >= 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

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

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

Policy # 00472
Original Effective Date: 12/16/2015
Current Effective Date: 09/09/2024

The 95th 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

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

Policy # 00472
Original Effective Date: 12/16/2015
Current Effective Date: 09/09/2024

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. Clinical 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 (≥30mg/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. ≥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. ≥45% using the Framingham long-term CVD (MI, CHD death or stroke) risk calculator

 # Clinical ASCVD (includes one of more of the following):

I. Myocardial infarction (MI) or other acute coronary syndrome (ACS)
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 in symptomatic patients 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)

^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 (≥140/≥90 mm Hg) or on a blood pressure medication)
V. Low HDL-C
    A. Male < 40 mg/dL
    B. Female < 50 mg/dL

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

Policy # 00472
Original Effective Date: 12/16/2015
Current Effective Date: 09/09/2024

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 both PCSK9 products have cardiovascular outcomes data in patients with atherosclerotic cardiovascular disease who have LDL-C ≥ 70 mg/dL despite therapy. This policy already provides coverage for these members, so no changes in 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 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)

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. In early 2021, Praluent gained an indication as an adjunct to other LDL-C lowering therapies in adult patients with HoFH to reduce LDL-C. Praluent received its latest label update in March of 2024, now being indicated as an adjunct to diet and other LDL-C lowering therapies in pediatric patients aged 8 years and older with HeFH to reduce LDL-C.

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

In late 2021, Repatha's label was updated to allow usage in patients 10 years and older with FH. The Pediatric section of the package insert previously limited this to 13 years of age and older.

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.

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

Policy # 00472
Original Effective Date: 12/16/2015
Current Effective Date: 09/09/2024

Praluent Studies

Praluent 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, 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.

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 ≥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).

Study 7 was a multicenter, double-blind, placebo-controlled trial that randomly assigned 45 adult patients to Praluent 150 mg every 2 weeks and 24 adult patients to placebo. Patients were taking maximally tolerated doses of statins with or without other lipid-lowering therapy and required additional LDL-C reduction. Randomization was stratified by LDL apheresis treatment status. The diagnosis of HoFH was made by either clinical diagnosis, which included a history of an untreated total cholesterol concentration > 500 mg/dL together with either xanthoma before 10 years of age or with a history of total cholesterol > 250 mg in both parents, or by genetic testing. Mean baseline LDL-C was 283 mg/dL with 97% on statins, 72% on ezetimibe, and 14% on lomitapide. No patient discontinued from the study prior to the 12-week primary endpoint. At week 12, the treatment difference between Praluent and placebo in mean LDL-C percent change from baseline was -36% (95% CI: -51% to -20%; p < 0.0001). Patients with two LDL-receptor negative alleles (little to no residual function) had a minimal to absent response to Praluent.

Study 8 was a randomized, multicenter, placebo controlled, double blind, 24 week trial in 153 pediatric patients aged 8 to 17 years with HeFH. Patients were on a low-fat diet and receiving background lipid-lowering therapy. Patients were randomized in a 2:1 ratio to receive Praluent or placebo. In the Praluent group dosed every 2 weeks, 49 patients received a dose of 40 mg for body weight less than 50 kg or 75 mg for body weight 50 kg or more. In the Praluent group dosed every 4 weeks, 52 patients received a dose of 150 mg for body weight less than 50 kg or 300 mg for body weight 50 kg or more. Dose adjustment of Praluent to 75 mg every 2 weeks for body weight less than 50 kg or 150 mg every 2 weeks for body weight 50 kg or more occurred at week 12 in patients with LDL-C ≥110 mg/dL. At week 24 in the group receiving treatment every 4 weeks, the treatment difference between the Praluent and placebo groups in LS mean LDL-C percent change from baseline was -31.4% (97.5% CI: -45.0 to -17.9; p< 0.0001).

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, placebo-controlled, 52-week trial that included 901 patients with hyperlipidemia who received protocol-determined background lipid-lowering therapy of a cholesterol-lowering diet either alone or in addition to atorvastatin (10 mg or 80 mg daily) or the combination of atorvastatin 80 mg daily with ezetimibe. After stabilization on background therapy, patients were randomly assigned to the addition of placebo or Repatha 420 mg administered subcutaneously once monthly. After stabilization on the assigned background therapy, the mean baseline LDL-C ranged between 90 and 117 mg/dL across the four background therapy groups. In these patients with hyperlipidemia on a protocol-determined background therapy, the difference between Repatha 420 mg once monthly and placebo in mean percent change in LDL-C from baseline to Week 52 was −55% (95% CI: −60%, −50%; p < 0.0001).

Study 2 was a multicenter, double-blind, randomized, placebo- and active-controlled, 12-week trial that included 614 patients with hyperlipidemia who were not taking lipid-lowering therapy at baseline. Patients were randomly assigned to receive subcutaneous injections of Repatha 140 mg every 2 weeks, Repatha 420 mg once monthly, or placebo for 12 weeks. Blinded administration of ezetimibe was also included as an active control. The mean baseline LDL-C was 143 mg/dL. The

difference between Repatha and placebo in mean percent change in LDL-C from baseline to Week 12 was −55% (95% CI: −60%, −50%; p < 0.0001) and −57% (95% CI: −61%, −52%; p <0.0001) for the 140 mg every 2 weeks and 420 mg once monthly dosages, respectively. The difference between Repatha and ezetimibe in mean percent change in LDL-C from baseline to Week 12 was −37% (95% CI: −42%, −32%; p < 0.0001) and −38% (95% CI: −42%, −34%; p <0.0001) for the 140 mg every 2 weeks and 420 mg once monthly dosages, respectively.

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.

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; $p < 0.0001$).

Study 7 was a multicenter, open-label 5-year extension study with Repatha in 106 patients with HoFH, who were treated with Repatha as an adjunct to other lipid-lowering therapies. The study included 14 pediatric patients (ages 13 to 17 years). All patients in the study were initially treated with Repatha 420 mg once monthly except for those receiving lipid apheresis at enrollment, who began with Repatha 420 mg every 2 weeks. Dose frequency in non-apheresis patients could be titrated up to 420 mg once every 2 weeks based on LDL-C response and PCSK9 levels. A total of 48 patients with HoFH received Repatha 420 mg once monthly for at least 12 weeks in Study 7 followed by Repatha 420 mg every 2 weeks for at least 12 weeks. Mean percent change from baseline in LDL-C were -20% at week 12 of 420 mg once monthly treatment and -30% at week 12 of 420 mg every 2 weeks treatment, based on available data.

Study 8 was a randomized, multicenter, placebo-controlled, double-blind, 24-week trial in 157 pediatric patients aged 10 to 17 years with HeFH. Patients were required to be on a low-fat diet and optimized background lipid-lowering therapy. Patients were randomly assigned 2:1 to receive 24 weeks of subcutaneous once monthly Repatha 420 mg or placebo; 104 patients received Repatha and 53 patients received placebo. The mean age was 14 years (range: 10 to 17 years). The mean LDL-C at baseline was 184 mg/dL; 17% of patients were on high-intensity statin, 62% on moderate-

intensity statin, and 13% on ezetimibe. The difference between Repatha and placebo in mean percent change in LDL-C from baseline to week 24 was −38% (95% CI: −45%, −31%; $p < 0.0001$).

Study 9 was an open-label, single-arm, multicenter, 80-week study to evaluate the safety, tolerability, and efficacy of Repatha for LDL-C reduction in pediatric patients aged 10 to 17 years with HoFH. Patients were on a low-fat diet and receiving background lipid-lowering therapy. Overall, 12 patients with HoFH received Repatha 420 mg subcutaneously once monthly. The mean age was 12 years (range 11 to 17 years). Median (Q1, Q3) LDL-C at baseline was 398 (343, 475) mg/dL, and all patients were on statins (atorvastatin or rosuvastatin) and ezetimibe. No patients were receiving lipid apheresis. The median (Q1, Q3) percent change in LDL-C from baseline to week 80 was −14% (−41, 4). Two of the 3 subjects with < 5% LDLR activity responded to Repatha treatment.

References

1. Praluent [package insert]. Sanofi/Regeneron. Bridgewater, NJ/Tarrytown, NY. Updated March 2024.
2. Repatha [package insert]. Amgen. Thousand Oaks, CA. September 2021.
3. Kynamro solution for subcutaneous injection [prescribing information]. Cambridge, MA: Genzyme; March 2015.
4. Juxtapid capsules [prescribing information]. Cambridge, MA: Aegerion Pharmaceuticals; August 2014.
5. 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.
6. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered 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.
7. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1-full report. J Clin Lipidol. 2015;9:129-169.
8. 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.

9. Guyton JR, Bays HE, Grundy SM, Jacobson TA. An assessment by the Statin Intolerance Panel: 2014 update. J Clin Lipidol. 2014;8:S72-S81.
10. 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.
11. Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of statins in routine care settings. Ann Intern Med. 2013;158(7):526-534.
12. 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.
13. 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.
14. 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.
15. 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 67th Scientific Sessions; Orlando, FL; March 10-12, 2018. Presented March 10, 2018. Available at: http://www.acc.org/educationand-meetings/image-and-slide-gallery/media-detail?id=90e30055844c402ba16d54fb05e45136.
16. Schwartz GG, Bessac L, Berdan LG, et al. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of the ODYSSEY Outcomes trial. Am Heart J. 2014;168:682-689.e1.
17. Sabatine MS, Giugliano RP, Keech A, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017;376(18):1713-1722.
18. Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Covington AM, DePalma SM, Minissian MB, Orringer CE, Smith SC Jr, Waring AA, Wilkins JT. 2022 ACC expert consensus decision pathway on the role of nonstatin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2022;80:1366-1418.

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

Policy # 00472
Original Effective Date: 12/16/2015
Current Effective Date: 09/09/2024

Policy History

Original Effective Date: 12/16/2015
Current Effective Date: 09/09/2024

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
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.
06/03/2021	Medical Policy Committee review
06/09/2021	Medical Policy Implementation Committee approval. Added criteria for the new FDA approved dosing of Repatha 420 mg every 2 weeks for HoFH. Updated background information to reflect new dosing for both medications. Added new trial data for both medications.
09/02/2021	Medical Policy Committee review

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

Policy # 00472
Original Effective Date: 12/16/2015
Current Effective Date: 09/09/2024

09/08/2021	Medical Policy Implementation Committee approval. Added a requirement that clinical evidence or patient history suggesting the use of Repatha will be ineffective or cause an adverse reaction to the patient must be demonstrated prior to gaining access to Praluent.
01/06/2022	Medical Policy Committee review
01/12/2022	Medical Policy Implementation Committee approval. Updated the age for Repatha to 10 years of age for Familial Hypercholesterolemia. Updated appropriate sections to reflect this change. Added Nexletol and Nexlizet as medications that are not allowed in combination with PCSK9 inhibitors to match Policy 00714.
01/05/2023	Medical Policy Committee review
01/11/2023	Medical Policy Implementation Committee approval. No change to coverage.
06/01/2023	Medical Policy Committee review
06/14/2023	Medical Policy Implementation Committee approval. Updated clinical ASCVD language to clarify intent of policy.
08/01/2024	Medical Policy Committee review
08/14/2024	Medical Policy Implementation Committee approval. Updated the age for Praluent to 8 years of age for Heterozygous Familial Hypercholesterolemia. Updated statin requirements for a high intensity statin to be within the range of Crestor 20-40 mg and Lipitor 40-80 mg.

Next Scheduled Review Date: 08/2025

*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.

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

Policy # 00472
Original Effective Date: 12/16/2015
Current Effective Date: 09/09/2024

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.