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

Policy # 00472
Original Effective Date: 12/16/2015
Current Effective Date: 03/15/2017

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.

Patient Selection Criteria
Based on review of available data, the Company may consider alirocumab (Praluent) OR evolocumab (Repatha) when the following criteria are met:

Initial Authorization (1 year): (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 a PCSK9 inhibitor; AND
III. The requested PCSK9 inhibitor will NOT be used in combination with lomitapide (Juxtapid®) or mipomersen (Kynamro®); AND
IV. The requested PCSK9 inhibitor will be used along with a maximally tolerated statin [in those who are not considered statin intolerant (see below for statin intolerance)]; AND
V. Patient must meet one of the following (A, B, C, or D):
A. Patient has a diagnosis of familial hypercholesterolemia (FH), 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®) 40mg, atorvastatin (Lipitor®) 80mg] PLUS ezetimibe (Zetia®) 10mg daily for at least 3 months (Note that the 3 month timeframe and the addition of Zetia are additional company requirements and will be denied as not medically necessary if not met); OR
   ii. 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 maximally tolerated stable daily statin (of any potency) PLUS ezetimibe (Zetia®) 10mg daily for at least 3 months ONLY if proof is given that a high potency maximum daily dose statin was not well tolerated (Note
that the 3 month timeframe and the addition of Zetia are additional company requirements and will be denied as not medically necessary if not met; OR

B. Patient has a diagnosis of familial hypercholesterolemia (FH), 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] 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 a diagnosis of NON-familial hypercholesterolemia AND the presence of atherosclerotic cardiovascular disease; AND
   i. Patient’s low density lipoprotein cholesterol (LDL-C) is not adequately controlled [e.g. not at the LDL-C treatment goal of <70 mg/dL] based on the current National Lipid Association (NLA) guidelines with a high potency maximum daily dose statin [rosuvastatin (Crestor) 40mg, atorvastatin (Lipitor) 80mg] PLUS ezetimibe (Zetia) 10mg daily for at least 3 months (Note that the 3 month timeframe and the addition of Zetia are additional company requirements and will be denied as not medically necessary if not met); OR
   ii. Patient’s low density lipoprotein cholesterol (LDL-C) is not adequately controlled [e.g. not at the LDL-C treatment goal of <70 mg/dL] based on the current National Lipid Association (NLA) guidelines with a maximally tolerated stable daily statin (of any potency) PLUS ezetimibe (Zetia) 10mg daily for at least 3 months ONLY if proof is given that a high potency maximum daily dose statin was not well tolerated (Note that the 3 month timeframe and the addition of Zetia are additional company requirements and will be denied as not medically necessary if not met); OR

D. Patient has a diagnosis of NON-familial hypercholesterolemia AND the presence of atherosclerotic cardiovascular disease; AND
   i. Patient’s low density lipoprotein cholesterol (LDL-C) is not adequately controlled [e.g. not at the LDL-C treatment goal of <70 mg/dL] based on the current National Lipid Association (NLA) guidelines] due to statin intolerance; AND
Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) Inhibitors [alirocumab (Praluent®), evolocumab (Repatha™)]

Policy # 00472
Original Effective Date: 12/16/2015
Current Effective Date: 03/15/2017

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 (1 year): (Patient must meet I and II)
I. Patient previously met the initial criteria and received an approval for the requested drug; AND
II. Patient has achieved clinically significant LDL-C lowering AND is compliant with the requested drug.

When Services Are Considered Not Medically Necessary
Based on review of available data, the Company considers the use of PCSK9 inhibitors [alirocumab (Praluent) OR evolocumab (Repatha)] when the patient 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 PCSK9 inhibitors [alirocumab (Praluent) OR evolocumab (Repatha)] when the patient has not tried ezetimibe (Zetia) in addition to a statin to be not medically necessary.**

Based on review of available data, the Company considers the use of PCSK9 inhibitors [alirocumab (Praluent) OR evolocumab (Repatha)] when the re-authorization criteria is 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 PCSK9 inhibitors [alirocumab (Praluent) OR evolocumab (Repatha)] when patient selection criteria are not met (except those listed above as not medically necessary**) to be investigational.*
Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) Inhibitors [alirocumab (Praluent®), evolocumab (Repatha™)]

Policy # 00472
Original Effective Date: 12/16/2015
Current Effective Date: 03/15/2017

Background/Overview
Praluent and Repatha belong to a new class of medications known as the proprotein convertase subtilisin kexin type 9 (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 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. 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. The long term effects of Praluent on cardiovascular morbidity and mortality have yet to be determined.

Repatha is indicated 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. The recommended dose of Repatha for those with primary hyperlipidemia with established clinical atherosclerotic cardiovascular disease or heterozygous familial 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. The long term effects of Repatha on cardiovascular morbidity and mortality have yet to be determined.

Hypercholesterolemia/Treatment Guidelines
Approximately 30% of the United States population has elevated LDL-C (low density lipoprotein cholesterol). There is also a subset of hypercholesterolemia, known as familial hypercholesterolemia, which can affect nearly 1 in 300 individuals. Familial hypercholesterolemia 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. Per the package insert, these drugs are limited to those with only familial hypercholesterolemia OR those with non-familial hypercholesterolemia that have clinical atherosclerotic cardiovascular disease. 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 (World Health Organization)/Dutch Lipid Clinic Network Familial Hypercholesterolemia diagnostic criteria to determine if an individual had familial
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Policy # 00472  
Original Effective Date: 12/16/2015  
Current Effective Date: 03/15/2017

hypecholesterolemia. 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**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family history</strong></td>
<td></td>
</tr>
<tr>
<td>First-degree relative with known premature* coronary and vascular disease, OR</td>
<td>1</td>
</tr>
<tr>
<td>First-degree relative with known LDL-C level above the 95th percentile</td>
<td>1</td>
</tr>
<tr>
<td>First-degree relative with tendinous xanthomata and/or arcus cornealis, OR</td>
<td>2</td>
</tr>
<tr>
<td>Children aged less than 18 years with LDL-C level above the 95th percentile</td>
<td>2</td>
</tr>
<tr>
<td><strong>Clinical history</strong></td>
<td></td>
</tr>
<tr>
<td>Patient with premature* coronary artery disease</td>
<td>2</td>
</tr>
<tr>
<td>Patient with premature* cerebellar or peripheral vascular disease</td>
<td>1</td>
</tr>
<tr>
<td><strong>Physical examination</strong></td>
<td></td>
</tr>
<tr>
<td>Tendinous xanthomata</td>
<td>6</td>
</tr>
<tr>
<td>Arcus cornealis prior to age 45 years</td>
<td>4</td>
</tr>
<tr>
<td><strong>Cholesterol levels mg/dl (mmol/liter)</strong></td>
<td></td>
</tr>
<tr>
<td>LDL-C &gt;= 330 mg/dL (≥8.5)</td>
<td>8</td>
</tr>
<tr>
<td>LDL-C 250 – 329 mg/dL (6.5–8.4)</td>
<td>5</td>
</tr>
<tr>
<td>LDL-C 190 – 245 mg/dL (5.0–6.4)</td>
<td>3</td>
</tr>
<tr>
<td>LDL-C 155 – 189 mg/dL (4.0–4.9)</td>
<td>1</td>
</tr>
<tr>
<td><strong>DNA analysis</strong></td>
<td></td>
</tr>
<tr>
<td>Functional mutation in the LDLR, apo B or PCSK9 gene</td>
<td>8</td>
</tr>
<tr>
<td><strong>Diagnosis (Diagnosis is based on the total number of points obtained)</strong></td>
<td></td>
</tr>
<tr>
<td>Definite Familial Hypercholesterolemia</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Probable Familial Hypercholesterolemia</td>
<td>6 – 8</td>
</tr>
<tr>
<td>Possible Familial Hypercholesterolemia</td>
<td>3 – 5</td>
</tr>
<tr>
<td>Unlikely Familial Hypercholesterolemia</td>
<td>&lt;3</td>
</tr>
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</table>

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

Policy # 00472
Original Effective Date: 12/16/2015
Current Effective Date: 03/15/2017

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

The following link for the ATP III-A distribution of LDL Cholesterol in the US Adult 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.
Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) Inhibitors [alirocumab (Praluent®), evolocumab (Repatha™)]

Policy # 00472
Original Effective Date: 12/16/2015
Current Effective Date: 03/15/2017

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 (≥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

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

Policy #: 00472
Original Effective Date: 12/16/2015
Current Effective Date: 03/15/2017

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

Treatment Goals:

<table>
<thead>
<tr>
<th>Risk</th>
<th>LDL-C Treatment Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very High Risk</td>
<td>&lt;70 mg/dL</td>
</tr>
<tr>
<td>High Risk</td>
<td>&lt;100 mg/dL</td>
</tr>
</tbody>
</table>

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

Policy # 00472
Original Effective Date: 12/16/2015
Current Effective Date: 03/15/2017

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.

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.

It should be clearly noted that the long term effects of Praluent or Repatha on cardiovascular morbidity and mortality have yet to be determined.

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
The efficacy of Praluent was investigated in five double-blind, placebo controlled trials that enrolled 3,499 patients; 36% were patients with heterozygous familial hypercholesterolemia and 54% were non-familial hypercholesterolemia patients who had clinical atherosclerotic cardiovascular disease. Three of the five trials were conducted exclusively in patients with heterozygous familial hypercholesterolemia (HeFH). In the trials for patients with HeFH, the diagnosis was made either by genotyping or clinical criteria (“definite” FH using the Simon Broome or WHO/Dutch Lipid Network criteria). All trials were at least 52 weeks and the primary efficacy endpoint was measured at week 24 [mean percent change in LDL-C from baseline].

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

Policy # 00472
Original Effective Date: 12/16/2015
Current Effective Date: 03/15/2017

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).

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

Policy # 00472
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Current Effective Date: 03/15/2017

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.

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.

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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).

Next Scheduled Review Date: 03/2018

*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. 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 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.

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

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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.