Introduction

Familial hypercholesterolemia (FH) is a genetic disorder, which means it is passed down through families. FH is caused by a defect in a specific gene. Because of the defect, the body can’t remove LDL cholesterol (the “bad cholesterol”) from the blood. The result is a very high level of LDL. Untreated high levels of LDL can lead to deposits of fat and cholesterol on walls of the arteries. These plaques can narrow or block the arteries and cause heart and blood vessel disease. The first step to reduce LDL is a change in lifestyle, such as altering the diet and getting more exercise. If this does not work well enough, the next step is to use standard medications, such as atorvastatin or rosuvastatin, to reduce cholesterol. If cholesterol levels remain extremely high despite these types of medications, other types of cholesterol drugs may be prescribed. These drugs are known as PCSK9 inhibitors. This policy describes when a PCSK9 inhibitor may be approved after medical records show that these other treatments did not bring LDL cholesterol down to desired levels.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
# Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Indication</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial heterozygous hypercholesterolemia</td>
<td>Praluent® (alirocumab) and Repatha® (evolocumab) may be considered medically necessary for treatment of familial hypercholesterolemia (for primary prevention) when ALL FIVE of the following criteria have been met. In addition to meeting criteria for familial hypercholesterolemia, requests involving failure of statins due to myalgias or transaminitis will be considered medically necessary when criteria listed below are met (see criteria for myalgias and transaminitis). (Documentation from the patient’s chart is REQUIRED): 1. Patient is ≥ 18 years old <strong>AND</strong> 2. Diagnosis of familial heterozygous hypercholesterolemia is established by either:    - LDL-C level ≥ 190 mg/dL on optimal LDL-C lowering therapy prior to adding a PCSK9 Inhibitor, <strong>OR</strong>    - Genetic typing indicating the presence of familial hypercholesterolemia <strong>AND</strong> 3. Patient has tried both atorvastatin 80 mg daily, AND Crestor® (rosuvastatin) ≥ 20 mg daily for ≥ 8 continuous weeks and LDL-C level has not achieved a 50% reduction from baseline or remains ≥ 100 mg/dL <strong>AND</strong> 4. Praluent® (alirocumab) or Repatha® (evolocumab) is prescribed by, or in consultation with, a cardiologist or endocrinologist <strong>AND</strong> 5. High dose statin therapy is continued while receiving alirocumab or evolocumab therapy (unless not tolerated)</td>
</tr>
<tr>
<td>Familial homozygous hypercholesterolemia</td>
<td>Praluent® (alirocumab) and Repatha® (evolocumab) may be considered medically necessary for treatment of familial hypercholesterolemia (for primary prevention) when ALL FIVE</td>
</tr>
</tbody>
</table>
of the following criteria have been met. In addition to meeting criteria for familial hypercholesterolemia, requests involving failure of statins due to myalgias or transaminitis will be considered medically necessary when criteria listed below are met (see criteria for myalgias and transaminitis).

(Documentation from the patient’s chart is REQUIRED):
1. Patient is ≥ 18 years old
2. Diagnosis of familial hypercholesterolemia is established by:
   o Genetic typing indicating the presence of familial hypercholesterolemia
3. Patient has tried both atorvastatin 80 mg daily, AND Crestor® (rosuvastatin) ≥ 20 mg daily for ≥ 8 continuous weeks and LDL-C level has not achieved a 50% reduction from baseline or remains ≥ 100 mg/dL
4. Praluent® (alirocumab) or Repatha® (evolocumab) is prescribed by, or in consultation with, a cardiologist or endocrinologist
5. High dose statin therapy is continued while receiving alirocumab or evolocumab therapy (unless not tolerated)

Praluent® (alirocumab) and Repatha® (evolocumab) may be considered medically necessary for treatment of hyperlipidemia in patients > 18 with clinical atherosclerotic cardiovascular disease (ASCVD), when ALL FOUR of the following criteria have been met. In addition to meeting criteria for ASCVD, requests involving failure of statins due to myalgias or transaminitis will be considered medically necessary when criteria listed below are met (see criteria for myalgias and transaminitis).

(Documentation from the patient’s chart is REQUIRED):
1. Patient has a history of at least ONE of the following in order for a PCSK9 inhibitor to be used for secondary prevention:
   o Myocardial infarction (MI) or acute coronary syndrome (ACS)
### Indication

<table>
<thead>
<tr>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Stroke or transient ischemic attack (TIA)</td>
</tr>
<tr>
<td>o Coronary revascularization procedure</td>
</tr>
</tbody>
</table>

**AND**

2. LDL-C level ≥ 100 mg/dL on optimal LDL-C lowering therapy prior to adding a PCSK9 Inhibitor:
   - Patient has tried both atorvastatin 80 mg daily, AND Crestor® (rosuvastatin) ≥ 20 mg daily for ≥ 8 continuous weeks, and LDL-C level has not achieved a 50% reduction from baseline or remains ≥ 100 mg/dL

**AND**

3. High dose statin therapy is continued while receiving alirocumab or evolocumab therapy (unless not tolerated)

**AND**

4. Praluent® (alirocumab) or Repatha® (evolocumab) is prescribed by, or in consultation with, a cardiologist or endocrinologist

### Symptom

<table>
<thead>
<tr>
<th>Medical Necessity</th>
</tr>
</thead>
</table>

#### Myalgias

**In addition to meeting above-stated criteria for familial hypercholesterolemia or ASCVD requests involving failure of statins due to myalgias will be considered medically necessary when ALL of the following criteria have been met:**

- Patient has intolerable symptoms and Creatine Kinase (CK) is > 10 x Upper Limit of Normal (ULN)

**AND**

- Provider ruled out other potential causes for myopathy (example: concomitant use of interacting medications, hypothyroidism, reduced renal or hepatic function, rheumatologic disorders, steroid myopathy, vitamin D deficiency, or primary muscle disease)

#### Transaminitis

**In addition to meeting above-stated criteria for familial hypercholesterolemia or ASCVD requests involving failure of statins due to transaminitis (eg, elevated Liver Function Tests) will be considered medically necessary when ALL of the following criteria have been met:**

- Provider ruled out other potential causes for transaminitis, such
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>as presence of baseline elevations due to comorbid conditions, such as obesity, prediabetes, etc</td>
</tr>
<tr>
<td>AND</td>
<td>Transaminitis persists beyond the 12-week period from the start of statin therapy</td>
</tr>
<tr>
<td>AND</td>
<td>Patient failed reduction of statin therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indication</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indications not listed in this policy</td>
<td>All uses of Praluent® (alirocumab) and Repatha® (evolocumab) for indications not listed in the Medical Necessity sections above are considered investigational.</td>
</tr>
</tbody>
</table>

**Praluent® (alirocumab) and Repatha® (evolocumab) Reauthorization**

Initial approval is valid for 12 months. Reauthorization requires documentation of ALL of the following:

1. Continued clinical benefit (ie, at goal LDL-C values- specific to the patient)
   
   **AND**

2. Praluent® (alirocumab) or Repatha® (evolocumab) is prescribed by, or in consultation with, a cardiologist or endocrinologist
   
   **AND**

3. The patient continues to receive the maximum tolerated dose of a statin while receiving alirocumab or evolocumab therapy

**Coding**

N/A

**Related Information**
Familial Hypercholesterolemia

Familial Hypercholesterolemia encompasses a group of genetic defects that causes severe elevations in LDL-C levels, as well as other lipid parameters. Heterozygous familial hypercholesterolemia (HeFH) occurs in roughly 1 in 300 to 500 patients, and is present in childhood. Total cholesterol levels in HeFH range from 350 to 550 mg/dL, which can result in premature ASCVD. Aggressive lipid-lowering therapy is recommended to achieve LDL-C reductions of at least 50%. Both children and adults with LDL-C levels of ≥ 190 mg/dL, following lifestyle modifications will require medication therapy. Statins are the initial treatment for all adults with FH. Higher risk patients may require intensification of drug therapy to achieve the more aggressive treatment goals. Intensification of medication therapy should be considered if LDL-C remains ≥ 160 mg/dL, or if an initial 50% reduction in LDL-C is not achieved. HeFH is a combination of genetic mutations in either the LDL receptor, or PCSK9 genes. Alterations in any of these genes are associated with reduced clearance of LDL-C from circulation leading to hyperlipidemia, collection of cholesterol in various tissues (tendons or eyes), and marked increased risk of cardiovascular disease. Homozygous familial hypercholesterolemia (HoFH) is much less common, the estimated U.S. prevalence being 1:1,000,000. These individuals usually present with untreated LDL-C > 650 mg/dL. Over 800 mutations are known to affect PCKS9 function, and they vary in severity. At this time, genetic testing of all patients is not standard practice, since the individual patients’ severity is indicated by the baseline untreated LDL-C.

Clinical Atherosclerotic Cardiovascular Disease

Atherosclerosis is responsible for almost all cases of coronary heart disease (CHD). Many factors are associated with an increased risk of atherosclerotic plaques in coronary arteries. Family history is an independent risk factor for CHD and is very important to be aware of, as the risk of developing CHD in the presence of positive family history can range from 15% to 100%, as has been shown in the cohort analyses done by various groups (eg, Physician’s Health Study, Women’s Health Study, Reykjavik Cohort Study, Framingham Offspring Study, INTERHEART Study, Cooper Center Longitudinal Study, Danish national population database). Other risk factors include, lifestyle (smoking, diet, exercise habits, etc.), as well as comorbid conditions, such as diabetes, kidney disease, thyroid disease, hypertension, etc. It is important to realize that lifestyle modifications are controllable risk factors, while positive family history is not. Atherosclerotic CV disease can manifest as coronary heart disease, carotid artery disease, peripheral arterial disease, and chronic kidney disease.
### Statin-Associated Adverse Events

Statins are both effective and generally safe, however, muscle toxicity remains a concern. Muscle syndromes associated with statins include, myalgias and muscle injury, or clinical rhabdomyolysis (rare). Other statin side effects may include hepatic dysfunction (elevation of aminotransferases), renal dysfunction (proteinuria), behavioral and cognitive changes, such as memory loss (still questionable). Side effect profile of each statin may be slightly different as lipophilicity/hydrophilicity properties of statins differ and can play a role. While statin chemical properties are one of the risk factors (which can be manipulated by switching patient to a different statin), others include: drug-drug interactions (CYP 450 inhibitors), comorbid medical conditions (eg, hypothyroidism, acute renal failure, biliary obstruction). Side effects can also be associated with dose-intensity and dosing schedule. In general, neuromuscular and skeletal adverse reactions for high-intensity statins (atorvastatin and Crestor® (rosuvastatin) have a 4% to 8% rate of occurrence.

### ACC/AHA Guidelines on Categorization of Statin Intensity

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL-C, on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL-C, on average, by approximately 30% to &lt;50%</td>
<td>Text Daily dose lowers LDL-C, on average, by &lt;30%</td>
</tr>
<tr>
<td>Atorvastatin (40†)–80 mg</td>
<td>Atorvastatin 10 (20 ) mg</td>
<td>Simvastatin 10 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20 (40) mg</td>
<td>Rosuvastatin (5 ) 10 mg</td>
<td>Pravastatin 10–20 mg</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20–40 mg‡</td>
<td>Lovastatin 20 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40 (80 ) mg</td>
<td>Fluvastatin 20–40 mg</td>
</tr>
<tr>
<td></td>
<td>Lovastatin 40 mg</td>
<td>Pitavastatin 1 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin XL 80 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluvastatin 40 mg BID</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 2–4 mg</td>
<td></td>
</tr>
</tbody>
</table>

### Benefit Application

The drugs included in this policy may be managed through either the pharmacy or medical benefit.
Alirocumab (Praluent®) and Evolocumab (Repatha®)

Alirocumab and evolocumab are proprotein converterase subtilisin kexin type 9 (PCSK9) inhibitors. PCSK9 is an enzyme that acts as part of the cholesterol homeostasis process in humans. PCSK9 binds to the epidermal growth factor-like domain of the LDL receptor on human hepatocytes. This binding forces LDL receptors to remain in the “open” confirmation, which facilitates their destruction, limiting the ability of the liver to remove LDL cholesterol from circulation. Humans with loss of function mutations in PCSK9 have notable lower LDL-C concentrations, and somewhat lower risk of cardiovascular disease.

The recommended starting dose of alirocumab is 75 mg administered SQ once every 2 weeks, since the majority of patients achieve sufficient LDL-C reduction with this dosage. If the LDL-C response is inadequate, the dosage may be increased to the maximum dosage of 150 mg administered every 2 weeks. Measure LDL-C levels within 4 to 8 weeks of initiating or titrating alirocumab, to assess response and adjust the dose, if needed.

The recommended dosing of evolocumab for primary hyperlipidemia with established clinical atherosclerotic CVD or HeFH is 140 mg every 2 weeks or 420 mg once monthly, administered SQ in abdomen, thigh, or upper arm. For HoFH, the dose is 420 mg once monthly. To administer 420 mg, give 3 REPATHA injections consecutively within 30 minutes.

Efficacy

The efficacy of alirocumab was investigated in five double-blind placebo-controlled trials that enrolled 3499 patients: 36% were patients with heterozygous familial hypercholesterolemia (HeFH), and 54% were non-FH patients, who had clinical atherosclerotic cardiovascular disease. Three of the five trials were conducted exclusively in patients with HeFH. All patients were receiving a maximally tolerated dose of a statin, with or without other lipid-modifying therapies. In the trials that enrolled patients with HeFH, the diagnosis of HeFH was made either by genotyping or clinical criteria (“definite FH” using either the Simon Broome or WHO/Dutch Lipid Network criteria). All trials were at least 52 weeks in duration with the primary efficacy endpoint measured at week 24 (mean % change in LDL-C from baseline). Three studies used an initial dose of 75 mg every 2 weeks (Q2W), followed by criteria-based up-titration to 150 mg Q2E at
week 12 for patients who did not achieve their pre-defined target LDL-C at week 8. The majority of patients (57% to 83%), who were treated for at least 12 weeks, did not require up-titration. Two studies used only a 150 mg Q2W dose.

Study 1 was a multicenter, double-blind, placebo-controlled trial that randomly assigned 1553 patients to alirocumab 150mg Q2W and 788 patients to placebo. All patients were taking maximally tolerated doses of statins with or without other lipid-modifying therapy, and required additional LDL-C reduction. The mean age was 61 years (range 18-89), 38% were women, 93% were Caucasian, 3% were Black, and 5% were Hispanic/Latino. Overall, 69% were non-FH patients with clinical atherosclerotic cardiovascular disease, and 18% had HeFH. The average LDL-C at baseline was 122 mg/dL. The proportion of patients who prematurely discontinued study drug prior to 24-week endpoint was 8% among those treated with the active drug, and 8% among those treated with placebo. At week 24, the treatment difference between alirocumab and placebo in mean LDL-C % change was -58% (95% CI: -61%, -56%; p-value: <0.0001).

Study 2 was a multicenter, double-blind, placebo-controlled trial that randomly assigned 209 patients to alirocumab and 107 to placebo. Patients were taking maximally tolerated doses of statins with or without other lipid-modifying therapy, and required additional LDL-C reduction. The mean age was 63 years (range 39-87), 34% were women, 82% were Caucasian, 16% were Black, and 11% were Hispanic/Latino. Overall 84% had clinical atherosclerotic cardiovascular disease. Mean baseline LDL-C was 102 mg/dL. The proportion of patients who prematurely discontinued study drug prior to the 24-week endpoint was 11% among those treated with alirocumab, and 12% among those treated with placebo. At week 12, the mean % change from baseline in LDL-C was -45% with active drug compared to 1% with placebo, and the treatment difference between alirocumab 75mg Q2W and placebo in mean LDL-C % change was -46% (95% CI: -53%, -39%). At week 12, if additional LDL-C lowering was required based on pre-specified LDL-C criteria, alirocumab was up-titrated to 150mg Q2W for the remainder of the trial. At week 24, the mean % change from baseline in LDL-C was -44% with active drug and 2% with placebo, and the treatment difference between alirocumab and placebo in mean LDL-C % change was =43% (95% CI: -50%, -35%; p-value: <0.0001). The dose was up-titrated to 150 mg Q2W in 32 (17%) of 191 patients treated with alirocumab for at least 12 weeks.

Studies 3 and 4 were multicenter, double-blind, placebo-controlled trials that, combined, randomly assigned 490 patients to alirocumab and 245 to placebo. The trials were similar with regard to both design and eligibility criteria. All patients had HeFH, were taking a maximally tolerated dose of statin with or without other lipid-modifying therapy, and required additional LDL-C reduction. The mean age was 52 years (range 20-87), 45% were women, 94% were Caucasian, 1% Black, and % were Hispanic/Latino. Overall, 45% of these patients with HeFH also
had clinical atherosclerotic cardiovascular disease. The average LDL-C at baseline was 141 mg/dL. Considering both trials together, the proportion of patients who prematurely discontinued study drug prior to the 24-week endpoint was 6% among those treated with active drug, and 4% among those treated with placebo. At week 12, the treatment difference between alirocumab 75mg Q2W and placebo in mean LDL-C % change was -48% (95% CI: -52%, -44%). At week 12, if additional LDL-C lowering was required based on pre-specified LDL-C criteria, alirocumab was up-titrated to 150mg Q2W for the remainder of the trials. At week 24, the mean treatment difference between alirocumab and placebo in mean LDL-C % change from baseline was -54% (95% CI: -59%, -50%; p-value: <0.0001). The dose was up-titrated to 150mg Q2W in 196 (42%) of 469 patients treated with alirocumab for at least 12 weeks. The LDL-C lowering effect was sustained to week 52.

Study 5 was a multicenter, double-blind, placebo-controlled trial that randomly assigned 72 patients to alirocumab 150mg Q2W and 35 patients to placebo. Patients had HeFH with a baseline LDL-C ≥ 160 mg/dL, while taking a maximally tolerated dose of statin with or without other lipid-modifying therapy. The mean age was 51 years (range 18-80), 47% were women, 88% were Caucasian, 2% were Black, and 6% were Hispanic/Latino. Overall, 50% had clinical atherosclerotic cardiovascular disease. The average LDL-C at baseline was 198 mg/dL. The proportion of patients who discontinued study drug prior to the 24-week endpoint was 10% among those treated with active drug, and 0% among those treated with placebo. At week 24, the mean % change from baseline in LDL-C was -43% with alirocumab, and -7% with placebo, and the treatment difference between alirocumab and placebo in mean LDL-C % change was -36% (95% CI: -49%, -24%; p-value: <0.0001).

Evidence for the efficacy of evolocumab stems from several phase III trials that are part of the extensive PROFICIO clinical trial program. The LAPLACE-2, OSLER and RUTHERFORD-2 trials were evaluated for this analysis. LAPLACE-2 randomized 2067 patients with hyperlipidemia to either evolocumab or ezetimibe with various strengths of statins. Evolocumab was associated with a greater reduction of LDL-C than did ezetimibe (-60% vs -23%). OSLER randomized 4465 patients from various “parent studies” to evolocumab plus standard therapy, or standard therapy alone to evaluate long-term safety. Long-term administration of evolocumab was associated with maintained greater LDL-C reduction than did standard therapy alone (P<.001). RUTHERFORD-2 randomized 331 patients with HeFH to either monthly evolocumab, biweekly evolocumab or placebo, in addition to statin therapy. Biweekly and monthly evolocumab were associated with greater reductions of LDL-C at 12 weeks than placebo (mean difference -59.2% and -61.3% respectively) (P<.0001). TESLA is the only study at this time evaluating evolocumab in patients with HoFH (N=50). Participants in the evolocumab arm experienced greater percent reductions in LDL-C than did placebo (-23.1% vs 7.9%; P<.0001).
Neither drug has any evidence of long-term clinical outcomes. Specifically, as noted in the label of both products, the effect of alirocumab and evolocumab on cardiovascular morbidity and mortality has not been determined.

**Cardiovascular Outcome Trials**

Evidence of long-term cardiovascular outcomes is based on two studies:

**FOURIER** was a randomized trial of evolocumab (140 mg every 2 weeks or 420 mg once per month) versus placebo in 27,564 patients with atherosclerotic disease on concurrent statin therapy. Follow-up was a median of 2.2 years. 76.8% (6337 of 8256 patients) in the evolocumab group and 76.8% (6337 of 8254 patients) in the placebo group. The primary end point was the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary end point was the composite of cardiovascular death, myocardial infarction, or stroke. Median duration of follow-up was 2.2 years. At 48 weeks, the least-squares mean percentage reduction in LDL cholesterol levels with evolocumab, as compared with placebo, was 59%, from a median baseline value of 92 mg per deciliter (2.4 mmol per liter) to 30 mg per deciliter (0.78 mmol per liter) (P<0.001). Relative to placebo, evolocumab treatment significantly reduced the risk of the primary end point (1344 patients [9.8%] vs. 1563 patients [11.3%]; hazard ratio, 0.85; 95% confidence interval [CI], 0.79 to 0.92; P<0.001) and the key secondary end point (816 [5.9%] vs. 1013 [7.4%]; hazard ratio, 0.80; 95% CI, 0.73 to 0.88; P<0.001). The results were consistent across key subgroups, including the subgroup of patients in the lowest quartile for baseline LDL cholesterol levels (median, 74 mg per deciliter [1.9 mmol per liter]). There was no significant difference between the study groups with regard to adverse events (including new-onset diabetes and neurocognitive events), with the exception of injection-site reactions, which were more common with evolocumab (2.1% vs. 1.6%). Inhibition of PCSK9 with evolocumab on a background of statin therapy lowered LDL cholesterol levels to a median of 30 mg per deciliter (0.78 mmol per liter) and reduced the risk of cardiovascular events. These findings show that patients with atherosclerotic cardiovascular disease benefit from lowering of LDL cholesterol levels below current targets.

Outcomes evidence for alirocumab was obtained from the ODYSSEY outcomes trial presented at the American College of Cardiology’s 2018 Scientific Session in March, 2018. The trial was a multi-site RCT testing alirocumab versus placebo in patients age ≥ 40 years, hospitalized for ACS with MI or unstable angina 1-12 months prior to randomization. A run-in period of 2-16 weeks of high-intensity or maximally tolerated dose of atorvastatin or rosuvastatin preceded the intervention period. Following the run-in period, subjects had to meet at least one of the following: LDL-C ≥ 70 mg/dL, Non-HDL-C ≥ 100 mg/dL, or Apolipoprotein B ≥ 80 mg/dL.
The primary outcome was a composite of coronary heart disease death, non-fatal MI, ischemic stroke (fatal and non-fatal), and hospitalization for unstable angina. The incidence of the primary outcome was lower in the alirocumab arm of the trial (hazard ratio (HR) 0.85, 95% CI 0.78-0.93). There was a non-significant reduction in CHD death (HR 0.92) and cardiovascular disease death (HR 0.88) and a nominally significant reduction in all-cause mortality (HR 0.85, 95% CI (0.73-0.98)). In the subgroup of patients with a high LDL-C level (≥100 mg/dL) on maximally tolerated statin therapy, the HR for all-cause mortality was 0.71 and for CV mortality was 0.69. There were statistically significant reductions in the HR for the primary outcome and key secondary mortality outcomes for patients in the high LDL-C group, as well as an improvement in clinical benefit over time in a landmark analysis.

**Safety**

The safety of alirocumab was evaluated in 9 placebo-controlled trials that included 2476 patients treated with alirocumab, including 2135 exposed for 6 months, and 1999 exposed for more than 1 year (median treatment duration of 65 weeks). The mean age of the population was 59 years, 40% of the population were women, 90% were Caucasians, 4% Black or African American, and 3% were Asians. At baseline, 37% of patients had a diagnosis of heterozygous familial hypercholesterolemia and 66% had clinical atherosclerotic cardiovascular disease. Adverse reactions reported in at least 2% of alirocumab-treated patients, and more frequently than in placebo-treated patients:

Long-term evolocumab safety data is from the OSLER study in which 4465 patients from 1 of 12 “parent” studies were randomized to either evolocumab and standard therapy, or standard therapy alone. In order to be eligible, patients must not have had adverse events leading to study discontinuation in the “parent” study. There was no placebo in the standard therapy arm. After 4219.4 patient-years of follow-up (median follow-up 11.1 months) adverse events occurred with similar frequency in both groups. Adverse events more common in the evolocumab group included neurocognitive events (0.9% vs 0.3%), arthralgia (4.6% vs 3.2%), and injection site reaction (4.3% vs N/A).

While not expressly studied, theoretical risks of the use of PCSK9 inhibition were noted by the Pharmacy and Therapeutics Committee. The clinical relevance of rapid, drastic reductions of LDL-C are unknown. Furthermore, LDL sequestration into hepatocytes by this mechanism could increase the risk of non-alcoholic fatty liver (NAFL) or possibly lead to drug induced non-alcoholic steatohepatits (NASH). Concern stems from the rapid introduction of LDL-C into hepatocytes while LDL clearance is unknown, combined with expert opinion that states that NAFL and NASH can develop without outward symptoms or abnormal laboratory values.
Furthermore, the theoretical risk of gallstones, masses of cholesterol precipitating in the gall bladder, cannot be ruled out with given trial data.

2018 Update

A literature search was conducted from 1/1/17 to 10/31/18. Outcomes evidence from the FOURIER and ODYSSEY Outcomes trials was added; however, there is no change to the medical necessity criteria, as the results of these trials confirm and do not alter earlier projections based on initial short-term studies.

References


### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>08/05/15</td>
<td>New policy, add to Pharmacy subsection. Considered medically necessary as an adjunct to diet and maximally tolerated statin therapy treatment for adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic CVD when criteria are met.</td>
</tr>
<tr>
<td>09/14/15</td>
<td>Interim update. Policy updated with recently FDA-approved drug, evolocumab (Repatha®). Heterozygous removed from policy statement; criteria numbered for improved clarity. References 8-14 added. “Inhibitors” added to policy title.</td>
</tr>
<tr>
<td>03/01/16</td>
<td>Interim update, approved February 18, 2016. Policy updated with guidelines around management of statin-induced myopathy, as well as statin-induced transaminitis.</td>
</tr>
<tr>
<td>09/13/16</td>
<td>Policy moved into new format; no change to policy statements. Corrected formatting to show that criteria for myalgias and transaminitis apply to both FH and ASCVD.</td>
</tr>
<tr>
<td>07/01/17</td>
<td>Annual Review, approved June 13, 2017. Updated ASCVD diagnoses criteria to exclude angina. Created two sections for FH, homozygous and heterozygous. Specified when a PCSK9 inhibitor might be used for primary vs. secondary prevention.</td>
</tr>
<tr>
<td>05/01/18</td>
<td>Interim Review, approved April 3, 2018. Medical Necessity criteria language revised for clear intent; no clinical criteria changes made. Note regarding “effect of alirocumab or evolocumab on cardiovascular morbidity and mortality has not been determined” was removed.</td>
</tr>
</tbody>
</table>
Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2018 Premera All Rights Reserved.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:

- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at: https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at:

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

Arabic (Arabic):

يحتوي هذا الإشعار على معلومات هامة. قد يحتوي هذا الإشعار على معلومات مهمة عن الخدمات والسياسات التي تقدمها Premera Blue Cross. يتعين عليك مراجعة هذه المعلومات واتخاذ إجراءات في حال وجود نزاع أو ارتباك.

800-722-1471 (TTY: 800-842-5357) مجاناً

中文 (Chinese):

本通知有重要的讯息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保單的重要訊息。本通知可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或者費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357).

Oromo (Cushite):


Français (French):


Kreyòl ayisyen (Creole):

Avi sila a gen Enfòmasyon Empòtan ladann. Avi sila a kapab genyen enfòmasyon enpòtan konsèplan aplikasyon w lan oswa konèsan kouvètis ariana lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou pran kék aksyon avan sèten dat limit pou ka tenbe kouvètis ariana sante w la oswa pou yo ka ede w avek depans yo. Se dwa w pou rewewa enfòmasyon sa a ak asisants nan lanyou ou pale a, san ou pa gen pou peye pounou sa. Rake nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):


Hmoob (Hmong):

Tseb ntwaw tshaj xo no muaj cov ntsiab lus tseem ceeb. Tej zaum tsab ntwaw tshaj xo no muaj cov ntsiab lus tseem ceeb xog koj daim ntawv thov kev pab lus yoj koj chqev kev pab cuam los ntawv Premera Blue Cross. Tej zaum muaj cov hnub tseem ceeb cuam rau hauv daim ntawv no. Tej zaum koj koy yuav tau uu qee yam uas peb koj uas tis puup dhaav cov caaj nyong uas teev tseeg rau hauv daim ntawv no mas koj thaj yuav tau baais kev pab cuam kho mob los yoj kev pab them tej nqi kho mob ntawv. Koj muaj cai kom laww muab cov ntsiab lus no uas tau muab sau ua koj hom lus pub dawb rau koj. Hu rau 800-722-1471 (TTY: 800-842-5357).

Iloko (Ilocano):

Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabalbin nga adda ket naglaon iti napateg nga impormasion maipanggep iti aplikasyonowy no coverage babaen iti Premera Blue Cross. Daytoy ket mabalbin dagiti importante a petai iti daytoy a pakdaar. Mabalbin nga adda rumbeng nga aramidenyo nga addang sakbay dagiti partikular a naituding nga aldaw tapno mapagtalainadyo ti coverage tì salun-atyo wenno tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong iti bukodyo a pagasasao nga awan ti bayadanyo. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):

Este Aviso contiene información importante.
Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).