Proprotein Convertase Subtilisin Kexin 9 (PCSK9) Inhibitors: PRALUENT™ (alirocumab) and REPATHA™ (evolocumab) subcutaneous injections

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member’s specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as “Description” defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as “Criteria” defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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Description:

Praluent (alirocumab) 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 low-density lipoprotein cholesterol (LDL-C). The effect of Praluent (alirocumab) on cardiovascular morbidity and mortality has not been determined.

Repatha (evolocumab) is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C) and other LDL-lowering therapies (e.g. statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C. The effect of Repatha on cardiovascular morbidity and mortality has not been determined.
Proprotein Convertase Subtilisin Kexin 9 (PCSK9) Inhibitors: PRALUENT™ (alirocumab) and REPATHA™ (evolocumab) subcutaneous injections (cont.)

Under normal physiological conditions, LDL-C is removed from the blood when it binds to an LDL receptor (LDLR) on the hepatocyte surface. Each LDLR binds a single LDL-C particle and is internalized into the hepatocyte. The LDL-C separates from the receptor and the unoccupied receptors are returned to the cell surface for reuse. At the same time, the lipoprotein is degraded and the released cholesterol is stored in the cell and used for a variety of cellular activities such as production of bile acids and very low density lipoproteins. The level of hepatic LDLR is controlled at the transcriptional level by proprotein convertase subtilisin kexin type 9 (PCSK9). Following its secretion, PCSK9 binds to LDLR and blocks the cholesterol-removal process by metabolizing the LDLR and breaking it up, effectively making it impossible for the LDLR to return to the surface of the cell and remove more cholesterol.

Praluent (alirocumab) is a human monoclonal antibody (IgG1 isotype) produced by recombinant DNA technology that inhibits PCSK9. PCSK9 is the enzyme responsible for removing LDLR from the hepatocyte surface. PCSK9 promotes the degradation of hepatic LDLR, which limits the ability of the liver to bind and remove LDL-C from the blood. Inhibition of PCSK9 increases the number of available LDLR, allowing for additional capacity to remove LDL-C from the bloodstream, leading to lowering of LDL-C levels.

Hypercholesterolemia is a major risk factor for atherosclerotic cardiovascular disease (ASCVD), which may result in one or more of the following: acute coronary syndrome (ACS), myocardial infarction (MI), stable or unstable angina, revascularization procedures, stroke or transient ischemic attack, and peripheral arterial disease that is atherosclerotic in origin. It usually results from nutritional factors such as a diet high in saturated fats combined with an underlying polygenic predisposition or it may be caused solely by a genetic disorder or a combination of other factors. Other risk factors include older age, early menopause in women, and family history of the condition.

Familial hypercholesterolemia (FH) is an autosomal-dominant genetic disorder. It is characterized by very high LDL-C levels requiring aggressive lipid-lowering in order to prevent cardiovascular disease. FH may be caused by mutations in any of several genes affecting receptor-mediated uptake of LDL-C, including the genes for the LDLR, the LDL receptor ligand (apolipoprotein B100, APOB), and PCSK9. The vast majority of people with FH have inherited a single mutation from one parent in either of these genes. A loss of function mutation in the LDLR gene results in absent or grossly malfunctioning LDLR and reduced uptake and clearance of circulating LDL-C by the liver.

Due to absence or abnormality in the LDLR in FH, the liver is unable to internalize LDL-C particles, leading to elevation in serum LDL-C levels. In turn, hepatic synthesis of cholesterol is not suppressed because LDL-C is not internalized by the hepatocytes. This leads to higher cholesterol production by the liver, despite already high levels of circulating cholesterol. As a result, circulating cholesterol levels increase dramatically. The elevated serum levels of LDL-C increases a LDL-C receptor-independent cholesterol uptake pathway in non-hepatic cells. This scavenger pathway allows cholesterol uptake by monocytes and macrophages, leading to foam cell formation, plaque deposition in the endothelium of coronary arteries, and premature coronary heart disease.

There are two forms of FH, heterozygous familial hypercholesterolemia (HeFH) and homozygous familial cholesterololemia (HoFH). HeFH is more common than HoFH, while HoFH is more severe. HeFH is estimated to occur in 1:300 to 1:500 individuals in the United States and Europe, while HoFH occurs in 1:1,000,000. Patients with HeFH can present with total cholesterol in the range of 350-550 mg/dL, while patients with HoFH can have total cholesterol in the range of 650-1000 mg/dL.
Proprotein Convertase Subtilisin Kexin 9 (PCSK9) Inhibitors: PRALUENT™ (alirocumab) and REPATHA™ (evolocumab) subcutaneous injections (cont.)

In all forms of FH, the phenotype is characterized by a high LDL-C level from birth, relatively normal high-density lipoprotein (HDL-C) and triglycerides, and early-onset coronary heart disease. Findings of FH on physical examination may include arcus corneae (a white ring around the cornea), xanthelasma (sharply demarcated yellowish deposits of fat underneath the skin), and tendon or tuberous xanthomas.

Medications currently approved for the treatment of hypercholesterolemia have been extensively studied, and many have long safety and efficacy track records. Patients with hypercholesterolemia are typically treated with statin therapy. Statins have been shown to reduce cardiovascular events and mortality. However, many patients are not able to achieve LDL goals on statin therapy alone. Other options that can be used with or without statin therapy include ezetimibe (Zetia), fibrates, niacin, and bile acid sequestrants. LDL apheresis is considered a standard of care in patients with HoFH, but may not be feasible due to patient access or tolerability. Other options for HoFH include mipomersen (Kynamro), lomitapide (Juxtapid), and now evolocumab (Repatha) which are typically used in patients who are not adequately controlled with or cannot receive LDL apheresis.

Approximately 3-10% of patients on statins may develop intolerance to the statin used. Intolerance is defined as an inability to take a statin because of muscle symptoms or elevated creatine kinase. Individuals may present with muscle weakness, aches, cramps, or flu-like symptoms. Other effects, such as, headache, sleep disorders, dyspepsia, nausea, rash, alopecia, erectile dysfunction, gynecomastia, and/or arthritis, may also contribute to a patient’s inability to take them. However, less than 1% of patients on statin therapy developed serious side-effects such as myopathy, myositis, or rhabdomyolysis.

Risk factors for statin intolerance and of developing muscle-related symptoms-although rare include, female gender, advanced age, patients with significant comorbidities (such as liver failure, kidney failure, or thyroid disease), family history of myopathy, and statin dose. In addition, many cases occur after patients are co-administered an interacting medication (such as azole antifungals, cimetidine, clarithromycin, erythromycin, or cyclosporine). Some patients will respond favorably to lowering the statin dose or switching to another statin or administering statins in an unconventional (eccentric) schedule such as every other day, every second day, every third day, or even weekly instead of daily. Studies have shown that 92% of patients can tolerate a second statin and 72.5% can successfully tolerate a third agent. Use of long acting statins weekly instead of daily resulted in 74% of patients able to tolerate continued statin use. However some patients cannot achieve optimal lowering of LDL-C despite these dose modifications or use of an alternative statin. A combination of statin plus non-statins therapy may be used as another alternative and can even provide reductions of LDL-C similar to those seen with high-dose statin regimens.

The risk of developing statin associated muscle symptoms (SAMS) is not identical across all statins. Studies have suggested that the risk of developing SAMS is highest with simvastatin, atorvastatin, and lovastatin. The risk of myopathy has been suggested to be lowest with pravastatin and fluvastatin, possibly because they are more hydrophilic and, as a result, have less muscle penetration.
Proprotein Convertase Subtilisin Kexin 9 (PCSK9) Inhibitors: PRALUENT™ (alirocumab) and REPATHA™ (evolocumab) subcutaneous injections (cont.)

**Definitions:**

**Diagnosis of Heterozygous familial hypercholesterolemia (HeFH):**

**World Health Organization Criteria**

<table>
<thead>
<tr>
<th>Family history</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>First degree relative with known premature CAD &amp;/or LDL-C &gt; 95th percentile</td>
<td>1</td>
</tr>
<tr>
<td>First degree relative with tendon xanthomata &amp;/or children &lt; 18 y with LDL-C &gt; 95th percentile</td>
<td>2</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Clinical history</th>
<th></th>
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<tbody>
<tr>
<td>Patient has premature CAD</td>
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</tr>
<tr>
<td>Patient has premature cerebral/ peripheral vascular disease</td>
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</table>

<table>
<thead>
<tr>
<th>Physical exam</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Tendon xanthomata</td>
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</tr>
<tr>
<td>Arcus cornealis age &lt; 45 y</td>
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</table>

<table>
<thead>
<tr>
<th>LDL-C</th>
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<tbody>
<tr>
<td>&gt; 330 mg/dL (&gt; 8.5 mmol/L)</td>
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</tr>
<tr>
<td>250-329 mg/dL (6.5-8.4 mmol/L)</td>
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<td>190-249 mg/dL (5.0-6.4 mmol/L)</td>
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</tr>
<tr>
<td>155-189 mg/dL (4.0-4.9 mmol/L)</td>
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</table>

<table>
<thead>
<tr>
<th>Score</th>
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<tbody>
<tr>
<td>Definite FH: Score &gt; 8</td>
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<tr>
<td>Probable FH: Score 6-8</td>
</tr>
<tr>
<td>Possible FH: Score 3-5</td>
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<tr>
<td>No diagnosis: Score &lt; 3</td>
</tr>
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</table>

Premature CAD: male before age 55, female before age 60

**Simon-Broome Register Diagnostic Criteria**

<table>
<thead>
<tr>
<th>Definite</th>
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<tbody>
<tr>
<td>TC &gt; 6.7 mmol/L or LDL-C &gt; 4.0 mmol/L in a child aged &lt; 16 y OR</td>
<td></td>
</tr>
<tr>
<td>TC &gt; 7.5 mmol/L or LDL-C &gt; 4.9 mmol/L in an adult (levels either pretreatment or highest on-treatment) PLUS</td>
<td></td>
</tr>
<tr>
<td>Tendon xanthomas in patient, or in first-degree relative (parent, sibling or child), or in second degree relative (grandparent, uncle, or aunt) OR</td>
<td></td>
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<tr>
<td>DNA-based evidence of an LDL-R mutation, familial defective APO B 100, or a PCSK9 mutation.</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Possible</th>
<th></th>
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<tbody>
<tr>
<td>TC &gt; 6.7 mmol/L or LDL-C &gt; 4.0 mmol/L in a child aged &lt; 16 y OR</td>
<td></td>
</tr>
<tr>
<td>TC &gt; 7.5 mmol/L or LDL-C &gt; 4.9 mmol/L in an adult (levels either pretreatment or highest on-treatment) AND</td>
<td></td>
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<tr>
<td>AT LEAST ONE OF THE FOLLOWING:</td>
<td></td>
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<tr>
<td>Family history of myocardial infarction: &lt; 50 y of age in second-degree relative or &lt; 60 y of age in first degree relative</td>
<td></td>
</tr>
<tr>
<td>Family history of raised TC: &gt; 7.5 mmol/L in adult first- or second-degree relative or &gt; 6.7 mmol/L in child or sibling aged &lt; 16 y.</td>
<td></td>
</tr>
</tbody>
</table>
Proprotein Convertase Subtilisin Kexin 9 (PCSK9) Inhibitors: PRALUENT™ (alirocumab) and REPATHA™ (evolocumab) subcutaneous injections (cont.)

WHO and Simon-Broome Register Diagnostic Criteria

<table>
<thead>
<tr>
<th>Four Major Statin Benefit Groups: 2013 Recommendations AHA/ACC Cholesterol Guidelines</th>
<th>Recommendation for Statin intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary prevention</strong></td>
<td></td>
</tr>
</tbody>
</table>
| -Clinical ASCVD | • High intensity if age ≤75 y  
  • Moderate intensity if age >75 y |
| **Primary prevention** | |
| -LDL-C ≥190 mg/dL | High-intensity statin |
| -Age 40-75 y LDL-C 70-189 mg/dL +DM & no clinical ASCVD | • Moderate intensity if low risk (10-y ASCVD risk <7.5%)  
  • High intensity if high risk (10-y ASCVD risk >7.5%) |
| -Age 40-75 y LDL-C 70-189 mg/dL -DM or clinical ASCVD | Moderate or high intensity (10-y ASCVD risk ≥7.5%) |

Statin Treatment Categorized by Intensity Using 2013 AHA/ACC Cholesterol Guidelines

<table>
<thead>
<tr>
<th>High Intensity</th>
<th>Moderate Intensity</th>
<th>Low Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL-C, on average, approximately ≥ 50%</td>
<td>Daily dose lowers LDL-C, on average, by approximately 30% to &lt; 50%</td>
<td>Daily dose lowers LDL-C, on average, by approximately &lt; 30%</td>
</tr>
</tbody>
</table>

Specific statins & doses below were evaluated in RCTs & demonstrated a reduction in major cardiovascular events

| Atorvastatin 80 mg | Atorvastatin 10 mg  
  Fluvastatin 40 mg bid  
  Lovastatin 40 mg  
  Pravastatin 40 mg  
  Rosuvastatin 10 mg  
  Simvastatin 20-40 mg b |
|---|---|---|
| Lovastatin 20 mg  
  Pravastatin 10-20 mg |

Statins & doses listed below are approved by FDA, but not tested in reviewed RCTs

| Rosuvastatin 40 mg | Atorvastatin 20 mg  
  Rosuvastatin 5 mg  
  Pravastatin 80 mg  
  Fluvastatin XL 80 mg  
  Pitavastatin 2-4 mg |
|---|---|
| Fluvastatin 20-40 mg  
  Pitavastatin 1 mg  
  Simvastatin 10 mg |

a Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in the IDEAL trial.

b Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by FDA due to the increased risk of myopathy, including rhabdomyolysis.

Drug related events:

**Ineffective / failure**

Use of a drug employing optimal doses (FDA-recommended doses) for optimal duration; where the condition being treated has not improved or worsened

A request for branded agent described in the coverage guideline due to drug failure or ineffectiveness will be assessed for potential approval with documentation of use of optimal dose / duration of the generic product and meeting other criteria within the coverage guideline. When the drug in question is a combination product, there must be documentation of failure / ineffectiveness of concurrent use (each
ingredient used at the same time) of individual generic components. When the drug in question is a low
dose formulation, there must be documentation of failure / ineffectiveness of low dose generic
formulation.

**Adverse Drug Event:** Allergic reaction / Hypersensitivity / Intolerance
Use of a drug produced a significant reaction where continued use of the drug places the individual at risk for
either lack of improvement or worsening of the condition being treated or at risk for harm and the concern is
documented in medical record. A significant adverse drug event is when an individual’s outcome is death,
life-threatening, hospitalization (initial or prolonged), disability resulting in a significant, persistent, or
permanent change, impairment, damage or disruption in the individuals’ body function/structure, physical
activities or quality of life, or requires intervention to prevent permanent impairment or damage.

**Allergic reaction / hypersensitivity** – may or may not involve the active ingredient. When the active
ingredient is involved, use of same or a chemically similar agent places the individual at risk for harm
when the same or chemically similar agent is used. The subsequent reaction may be the same as the
original reaction or a more exaggerated response may be seen, potentially placing the individual at even
greater risk for harm.

If the reaction occurred from the active/main generic ingredient; request for branded agent with same
active ingredient will not be considered unless it is proven (documented) that active ingredient did not
cause reaction and the request meets other criteria within the coverage guideline

**Intolerance** – these events represent circumstance(s) where use of a drug produced a significant reaction
and continued use may result in non-adherence to proposed therapy and this concern is documented in
medical record

**Contraindication**
Use of a drug that is not recommended by the manufacturer or FDA labelling

Use of any drug in the face of a contraindication is outside of the FDA and manufacturer’s labelled
recommendation and is considered investigational or experimental

**Non-adherence**
Individual does not follow prescribe regimen that places the individual at risk for lack of improvement or
worsening of the condition being treated and this concern is documented in medical record

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**Precertification:**

Precertification (Prior Authorization) is required for members with a Blue Cross Blue Shield of Arizona (BCBSAZ)
pharmacy benefit for medication(s) or product(s) indicated in this guideline.

This Pharmacy Coverage Guideline does not apply to FEP or other states’ Blues Plans.
Proprotein Convertase Subtilisin Kexin 9 (PCSK9) Inhibitors: PRALUENT™ (alirocumab) and REPATHA™ (evolocumab) subcutaneous injections (cont.)

Information about medications that require precertification is available at [www.azblue.com/pharmacy](http://www.azblue.com/pharmacy).

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Criteria:

See “Resources” section for FDA-approved dosage.

- Precertification for Praluent (alirocumab) or Repatha (evolocumab) requires completion of the specific request form in its entirety. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. Incomplete forms will be returned.

Criteria for Praluent (alirocumab):

- FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Praluent (alirocumab) is considered **medically necessary** as an adjunct to diet for individuals who have not achieved target LDL-C reduction despite maximally tolerated doses of lipid lowering therapy who have medical record documentation of ALL of the following:
  1. Individual is 18 years of age or older
  2. A diagnosis of **EITHER** of the following:
     - Clinical atherosclerotic cardiovascular disease including one or more of the following; acute coronary syndromes, history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin OR
     - Definite diagnosis of heterozygous familial hypercholesterolemia by either World Health Organization Criteria (score of greater than 8) or Simon-Broome Register Diagnostic Criteria
  3. Individual has failed a trial of at least 2 high-intensity maximally tolerated doses of HMG-CoA reductase inhibitors (or statins), as evidenced by: less than a 50% reduction from the individuals baseline LDL-C when the baseline is known, or if baseline is unknown with documented cardiovascular disease the LDL-C remains >/= 70mg/dl, or with no known cardiovascular disease the LDL-C remains >/= 100mg/dl and the individual has also taken an additional ezetimibe containing product when their LDL-C reduction could be lowered by an additional 18-25% to reach the final therapeutic goal. Each trial must be for at least 12 weeks (documentation of attempts is required)
     OR
     - Individual is statin intolerant as defined by the National Lipid Association Statin Intolerance Panel and includes ALL of the following:
Exclusion of any secondary cause(s) of muscle toxicity
Inability to tolerate at least 2 statins with at least one started at the lowest starting daily dose
Intolerable symptoms or abnormal biomarker changes are reversible upon discontinuation of statin, but reproducible by re-challenge unless clinically inappropriate AND
Re-trial of the same statin and a different statin using the highest tolerated statin dose along with ezetimibe or an ezetimibe containing product has not achieved an adequate reduction in LDL-C
Re-trial of the same statin and a different statin using the highest tolerated statin dose utilizing an eccentric statin dosing schedule (every other day, every second day, every third day, or even weekly instead of daily) along with an ezetimibe containing product and has not achieved an adequate reduction in LDL-C

OR

Individual has FDA labeled contraindications to use of statins (documentation of FDA labeled contraindication is required)

OR

Has a diagnosis of any proven statin-induced rhabdomyolysis

4. Individual is adherent with a lipid lowering diet and other life-style modifications such as exercise and smoking cessation for at least 3 months (documentation of adherence is required)

5. ALL of the following tests have been completed before initiation of treatment:
   - Current LDL-C
   - Baseline LDL-C (when available)
   - Complete metabolic panel

6. Absence of ALL of the following exclusions:
   - Severe renal impairment
   - Severe hepatic impairment
   - Woman of child bearing age is pregnant or is likely to become pregnant (a statin contraindication)
   - Woman is breast feeding an infant of child (a statin contraindication)
   - Drug-drug interactions that increase the risk for statin intolerance have been discontinued if clinically safe and appropriate to do so or their doses have been adjusted or the dose of the statin drug has been appropriately adjusted

7. Prescribing of Praluent is by a cardiologist

➢ Praluent (alirocumab) for all other indications not previously listed is considered experimental or investigational based upon:

1. Lack of final approval from the Food and Drug Administration, and
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
3. Insufficient evidence to support improvement of the net health outcome, and
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
5. Insufficient evidence to support improvement outside the investigational setting.
Proprotein Convertase Subtilisin Kexin 9 (PCSK9) Inhibitors:
PRALUENT™ (alirocumab) and REPATHA™ (evolocumab) subcutaneous injections
(cont.)

This includes but is not limited to the following:

- Primary prevention of ASCVD
- Primary prevention of ASCVD in patients who are statin-intolerant
- Individuals not at high risk for ASCVD
- When used with alirocumab, lomitapide, or mipomersen
- In individuals who have homozygous familial hypercholesterolemia
- Individuals who are already at goal for therapy

Criteria for Repatha (evolocumab):

- FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Repatha (evolocumab) is considered *medically necessary* as an adjunct to diet for individuals who have not achieved target LDL-C reduction despite maximally tolerated doses of lipid lowering therapy who have medical record documentation of ALL of the following:

1. Individual is 18 years of age or older

2. A diagnosis of **ONE** of the following:
   - Clinical atherosclerotic cardiovascular disease including one or more of the following: acute coronary syndromes, history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, or peripheral arterial disease presumed to be of atherosclerotic origin
   - Definite diagnosis of Heterozygous familial hypercholesterolemia by either World Health Organization (score of greater than 8) or Simon-Broome Register Diagnostic Criteria
   - Homozygous familial hypercholesterolemia confirmed by **ONE** of the following:
     - Genetic confirmation of a mutation in the low-density lipoprotein (LDL) receptor, ApoB, or PCSK9
     - An untreated LDL-C of greater than 500mg/dl (or treated LDL-C of greater than 300 mg/dl) with **EITHER**:
       - Cutaneous or tendon xanthoma before age 10
       - Documented evidence of heterozygous familial hypercholesterolemia in both biologic parents

3. Individual has failed a trial of at least 2 high-intensity maximally tolerated doses of HMG-CoA reductase inhibitors (or statins), as evidenced by: less than a 50% reduction from the individuals baseline LDL-C when the baseline is known, or if baseline is unknown with documented cardiovascular disease the LDL-C remains >/= 70mg/dl, or with no known cardiovascular disease the LDL-C remains >/= 100mg/dl and the individual has also taken an additional ezetimibe containing product when their LDL-C reduction could be lowered by an additional 18-25% to reach the final therapeutic goal. Each trial must be for at least 12 weeks (documentation of attempts is required).

**OR**
Proprotein Convertase Subtilisin Kexin 9 (PCSK9) Inhibitors: PRALUENT™ (alirocumab) and REPATHA™ (evolocumab) subcutaneous injections (cont.)

Individual is statin intolerant as defined by the National Lipid Association Statin Intolerance Panel and includes ALL of the following:

- Exclusion of any secondary causes of muscle toxicity
- Inability to tolerate at least 2 statins with at least one started at the lowest starting daily dose
- Intolerable symptoms or abnormal biomarker changes (CK levels, hepatic transaminases) are reversible upon discontinuation of statin, but reproducible by re-challenge unless clinically inappropriate AND
- Re-trial of the same statin or a different statin using the highest tolerated statin dose along with ezetimibe or an ezetimibe containing product has not achieved an adequate reduction in LDL-C
- Re-trial of the same statin or a different statin using the best tolerated statin dose utilizing an eccentric statin dosing schedule (every other day, every second day, every third day, or even weekly instead of daily) along with an ezetimibe containing product and has not achieved an adequate reduction in LDL-C OR
- Individual has FDA labeled contraindications to use of statins (documentation of FDA labeled contraindication is required) OR
- Has a diagnosis of any proven statin-induced rhabdomyolysis (documentation of laboratory values is required CK> 10 10xULN)).

4. Individual is adherent with a lipid lowering diet and other life-style modifications such as exercise and smoking cessation for at least 3 months (documentation of adherence is required)

5. ALL of the following tests have been completed before initiation of treatment:

- Current LDL-C
- Baseline LDL-C (when available)
- Complete metabolic panel

6. Absence of ALL of the following exclusions:

- Severe renal impairment
- Severe hepatic impairment
- Woman of child bearing age is pregnant or is likely to become pregnant (a statin contraindication)
- Woman is breast feeding an infant of child (a statin contraindication)
- Drug-drug interactions that increase the risk for statin intolerance have been discontinued if clinically safe and appropriate to do so or their doses have been adjusted or the dose of the statin drug has been appropriately adjusted

7. Prescribing of Repatha is by a cardiologist

Repatha (evolocumab) for all other indications not previously listed is considered experimental or investigational based upon:

1. Lack of final approval from the Food and Drug Administration, and
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
Proprotein Convertase Subtilisin Kexin 9 (PCSK9) Inhibitors: PRALUENT™ (alirocumab) and REPATHA™ (evolocumab) subcutaneous injections (cont.)

3. Insufficient evidence to support improvement of the net health outcome, and
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
5. Insufficient evidence to support improvement outside the investigational setting.

This includes but is not limited to the following:

- Primary prevention of ASCVD
- Primary prevention of ASCVD in patients who are statin-intolerant
- Individuals not at high risk for ASCVD
- When used with alirocumab, lomitapide, or mipomersen
- Individuals who are already at goal for therapy

Approval Duration for Praluent and Repatha:

- Initial Therapy: 3 months
- Renewal 12 months, provided that the individual’s LDL-C has reached therapeutic goal

Resources:


Proprotein Convertase Subtilisin Kexin 9 (PCSK9) Inhibitors:
PRALUENT™ (alirocumab) and REPATHA™ (evolocumab) subcutaneous injections (cont.)

FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
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<tbody>
<tr>
<td>PRALUENT is a PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) inhibitor antibody indicated as 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-cholesterol (LDL-C). Safety and efficacy in pediatric patients have not been established. The effect of PRALUENT (alirocumab) on cardiovascular morbidity and mortality has not been determined.</td>
<td>The recommended starting dose for Praluent is 75 mg administered subcutaneously 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 PRALUENT, to assess response and adjust the dose, if needed.</td>
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<tr>
<td>REPATHA is a PCSK9 (proprotein convertase subtilisin kexin type 9) inhibitor antibody indicated as an adjunct to diet and: • Maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical • Atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C). • Other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.</td>
<td>• Administer by subcutaneous injection • Primary hyperlipidemia with established clinical atherosclerotic CVD or HeFH: 140 mg every 2 weeks or 420 mg* once monthly in abdomen, thigh, or upper arm. • HoFH: 420 mg* once monthly. • To administer 420 mg*, give 3 REPATHA injections consecutively within 30 minutes. • See Dosage and Administration for important administration instructions.</td>
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