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 (high cholesterol). Untreated high levels of LDL can lead to deposits of fat and cholesterol (plaque) on walls of the arteries. Plaques can narrow or block the arteries and cause heart and blood vessel disease. The first step to reduce high cholesterol is change the diet and increase exercise. If this does not work well enough, the next step is to use standard drugs called statins. If cholesterol levels remain high after using statins, other types of cholesterol drugs may be prescribed. This policy describes when other drugs used to lower cholesterol may be considered medically necessary.

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.
<table>
<thead>
<tr>
<th>Drug / Indication</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Praluent® (alirocumab), Repatha® (evolocumab)</td>
<td>Praluent® (alirocumab) and Repatha® (evolocumab) may be considered medically necessary for treatment of familial hypercholesterolemia (for primary prevention) when ALL FOUR 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):</td>
</tr>
</tbody>
</table>
| Familial hypercholesterolemia | 1. Patient is ≥ 18 years old  
AND  
2. Diagnosis of familial hypercholesterolemia is established by either:  
o. Untreated LDL-C level ≥ 190 mg/dL,  
OR  
o. Genetic typing indicating the presence of familial hypercholesterolemia  
AND  
3. Patient has tried maximum tolerated doses of atorvastatin OR rosvastatin for ≥ 8 continuous weeks and LDL-C level remains ≥ 70 mg/dL  
AND  
4. High-intensity statin therapy is continued while receiving Praluent® (alirocumab) or Repatha® (evolocumab) therapy unless not tolerated or contraindicated. |
| Praluent® (alirocumab), Repatha® (evolocumab) | Praluent® (alirocumab) and Repatha® (evolocumab) may be considered medically necessary for treatment of hyperlipidemia in patients > 18 years of age with clinical atherosclerotic cardiovascular disease (ASCVD), when ALL THREE 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): |
| Clinical atherosclerotic cardiovascular disease (ASCVD) | |
**Drug / Indication** | **Medical Necessity**
--- | ---
1. Patient has a history of at least ONE of the following in order for a PCSK9 inhibitor to be used for secondary prevention:
   - Myocardial infarction (MI) or acute coronary syndrome (ACS)
   - Stroke or transient ischemic attack (TIA)
   - Coronary revascularization procedure
   - Diabetes
   - Peripheral arterial disease
   - Stable or unstable angina
   **AND**
2. Patient has tried maximum tolerated doses of atorvastatin OR rosuvastatin for ≥ 8 continuous weeks and LDL-C level remains ≥ 70 mg/dL
   **AND**
3. High-intensity statin therapy is continued while receiving Praluent® (alirocumab) or Repatha® (evolocumab) therapy unless not tolerated or contraindicated

**Ethyl ester of eicosapentaenoic acid (EPA)**

**Vascepa® (icosapent ethyl)**

Vascepa® (icosapent ethyl) may be considered medically necessary to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization when the following criteria are met:
- Patient is ≥ 18 years of age
- Triglyceride (TG) levels are ≥ 150 mg/dL
- Patient is on moderate-intensity or high-intensity statin therapy unless not tolerated or contraindicated (see criteria for myalgias and transaminitis).
- Patient has established cardiovascular disease
- Diabetes mellitus and 2 of the following additional risk factors for cardiovascular disease
  - Family history of premature ASCVD:
    - Males < 55 years of age
    - Females < 65 years of age
<table>
<thead>
<tr>
<th>Drug / Indication</th>
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<tbody>
<tr>
<td></td>
<td>o Tobacco Use</td>
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<tr>
<td></td>
<td>o Hypertension defined as:</td>
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<td></td>
<td>▪ BP ≥ 130 mmHg systolic or ≥ 80 mmHg diastolic on an antihypertensive medication</td>
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<td></td>
<td>o Renal dysfunction defined as:</td>
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<tr>
<td></td>
<td>▪ eGFR = 15 – 59 mL/min/1.73m² = CrCl &lt; 60 mL/min with or without albuminuria</td>
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<tr>
<td></td>
<td>AND</td>
</tr>
<tr>
<td></td>
<td>• The daily dose of Vascepa is 4 grams per day (taken as either four 0.5 gram capsules twice daily with food or two 1 gram capsules twice daily with food).</td>
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</tbody>
</table>

**Vascepa® (icosapent ethyl) may be considered medically necessary for the treatment of severe hypertriglyceridemia when the following criteria are met:**

- Patient is ≥ 18 years of age

**AND**

- Triglyceride (TG) levels are ≥ 500 mg/dL

**AND**

- Patient has tried and failed one of the following fibrate products:
  - Fenofibrate
  - Fenofibric acid
  - Gemfibrozil

**OR**

- Patient has tried and failed a prescription niacin extended-release product

**AND**

- The daily dose of Vascepa is 4 grams per day (taken as either four 0.5 gram capsules twice daily with food or two 1 gram capsules twice daily with food).

**Adenosine triphosphate-citrate lyase (ACL) inhibitors**

<p>| Nexletol™ (bempedoic acid), Nexlizet™ (bempedoic acid and ezetimibe) | Nexletol™ (bempedoic acid) and Nexlizet™ (bempedoic acid and ezetimibe) may be considered medically necessary for treatment of familial hypercholesterolemia (for primary prevention) when ALL FOUR of the following criteria have been met. In addition to meeting criteria for familial |</p>
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<tr>
<td><strong>Familial hypercholesterolemia</strong></td>
<td>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):</td>
</tr>
<tr>
<td></td>
<td>1. Patient is ≥ 18 years old AND 2. Diagnosis of familial hypercholesterolemia is established by either: o Untreated LDL-C level ≥ 190 mg/dL, OR o Genetic typing indicating the presence of familial hypercholesterolemia AND 3. Patient has tried maximum tolerated doses of atorvastatin OR rosuvastatin for ≥ 8 continuous weeks and LDL-C level remains ≥ 70 mg/dL AND 4. High-intensity statin therapy is continued while receiving Nexletol™ (bempedoic acid) or Nexlizet™ (bempedoic acid and ezetimibe) therapy unless not tolerated or contraindicated</td>
</tr>
</tbody>
</table>

<p>| <strong>Nexletol™ (bempedoic acid), Nexlizet™ (bempedoic acid and ezetimibe)</strong> | Nexletol™ (bempedoic acid) and Nexlizet™ (bempedoic acid and ezetimibe) may be considered medically necessary for treatment of hyperlipidemia in patients ≥ 18 years of age with clinical atherosclerotic cardiovascular disease (ASCVD), when ALL THREE 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): |
| <strong>Clinical atherosclerotic cardiovascular disease (ASCVD)</strong>               | 1. Patient has a history of at least ONE of the following: o Myocardial infarction (MI) or acute coronary syndrome (ACS) o Stroke or transient ischemic attack (TIA) o Coronary revascularization procedure o Diabetes |</p>
<table>
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<tr>
<th>Drug / Indication</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
|                   | o Peripheral arterial disease  
o Stable or unstable angina  
AND  
2. Patient has tried maximum tolerated doses of atorvastatin OR rosuvastatin for ≥ 8 continuous weeks and LDL-C level remains ≥ 70 mg/dL  
AND  
3. High-intensity statin therapy is continued while receiving Nexletol™ (bempedoic acid) or Nexlizet™ (bempedoic acid and ezetimibe) therapy unless not tolerated or contraindicated |

**Microsomal Triglyceride Transfer Protein Inhibitor**

**Juxtapid® (lomitapide)**

**Homozygous familial hypercholesterolemia**

Juxtapid® (lomitapide) may be considered medically necessary for treatment of homozygous familial hypercholesterolemia (for primary prevention) when ALL FIVE of the following criteria have been met. In addition to meeting criteria for homozygous 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  
AND  
2. Diagnosis of homozygous familial hypercholesterolemia is established by either:  
o Documented functional mutation(s) in both LDL receptor alleles or alleles known to affect LDL receptor functionality  
OR  
o Skin fibroblast LDL receptor activity < 20% normal  
OR  
o Untreated TC > 500 mg/dL and TG < 300 mg/dL and both parents with documented untreated TC > 250 mg/dL  
AND  
3. Patient has tried maximum tolerated doses of atorvastatin OR rosuvastatin for ≥ 8 continuous weeks and LDL-C level remains ≥ 70 mg/dL  
AND
<table>
<thead>
<tr>
<th>Drug / Indication</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| 4. Patient has tried and failed Praluent® (alirocumab) or Repatha® (evolocumab) therapy unless not tolerated or contraindicated  
**AND**  
5. High-intensity statin therapy is continued while receiving Juxtapid® (lomitapide) therapy unless not tolerated or contraindicated. |

| HMG-CoA reductase inhibitors (statins) | Ezallor™ Sprinkle (rosuvastatin), Livalo® (pitavastatin), Nikita™ (pitavastatin), and Zypitamag™ (pitavastatin) may be considered medically necessary for the treatment of hyperlipidemia when patient has had a trial and treatment failure, or intolerance of any 2 of the following generic drugs:  
- Atorvastatin, simvastatin, lovastatin, pravastatin, rosuvastatin, or fluvastatin |
| Ezallor™ Sprinkle (rosuvastatin), Livalo® (pitavastatin), Nikita™ (pitavastatin), and Zypitamag™ (pitavastatin) may be considered medically necessary for the treatment of hyperlipidemia when patient has had a trial and treatment failure, or intolerance of any 2 of the following generic drugs:  
- Atorvastatin, simvastatin, lovastatin, pravastatin, rosuvastatin, or fluvastatin |
| Initial approval will be for three years. |
| Re-authorization criteria:  
- Documentation of continued clinical benefit (ie, at goal LDL-C values specific to the patient) |
| Flolipid (simvastatin oral suspension), Simvastatin oral suspension | Flolipid (simvastatin oral suspension) and brand simvastatin oral suspension may be considered medically necessary for the treatment of hyperlipidemia when patient has documentation in the form of medical records of the following:  
- At least a 3-month trial and treatment failure of 2 generic statins (atorvastatin, simvastatin, lovastatin, pravastatin, rosuvastatin, or fluvastatin)  
**OR**  
- Documentation that liquid is clinically necessary (eg, trouble swallowing, etc.) |

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myalgias</td>
<td>In addition to meeting above-stated criteria for familial hypercholesterolemia or ASCVD requests involving failure of</td>
</tr>
</tbody>
</table>
### Symptom

Statins due to myalgias will be considered medically necessary when ALL of the following criteria have been met:

- Patient has intolerable symptoms
- Provider ruled out other potential causes for myopathy (example: concomitant use of interacting medications, hypothyroidism, reduced renal or hepatic function, 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 as presence of baseline elevations due to comorbid conditions, such as obesity, prediabetes, etc
- Transaminitis persists beyond the 12-week period from the start of statin therapy
- Patient failed reduction of statin therapy

### Drug

**Juxtapid® (lomitapide), Nexletol™ (bempedoic acid), Nexlizet™ (bempedoic acid and ezetimibe), Praluent® (alirocumab), Repatha® (evolocumab), and Vascepa® (icosapent ethyl)**

### Investigational

All uses of Juxtapid® (lomitapide), Nexletol™ (bempedoic acid), Nexlizet™ (bempedoic acid and ezetimibe), Praluent® (alirocumab), Repatha® (evolocumab), and Vascepa® (icosapent ethyl) for indications not listed in the Medical Necessity sections above are considered investigational.
## Drug

<table>
<thead>
<tr>
<th>Drug</th>
<th>Not Medically Necessary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezallor™ Sprinkle (rosuvastatin), Flolipid (simvastatin oral suspension), Livalo® (pitavastatin), Nikita™ (pitavastatin), Simvastain oral suspension, Zypitamag™ (pitavastatin)</td>
<td>All uses of Ezallor™ Sprinkle (rosuvastatin), Flolipid (simvastatin oral suspension), Livalo® (pitavastatin), Nikita™ (pitavastatin), simvastatin oral suspension (brand), and Zypitamag™ (pitavastatin) not listed in the Medical Necessity sections above are considered not medically necessary.</td>
</tr>
</tbody>
</table>

## Length of Approval

<table>
<thead>
<tr>
<th>Approval</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial authorization</td>
<td>Unless noted otherwise for specific drugs under the medical necessity criteria the drugs listed in policy may be approved up to 12 months.</td>
</tr>
</tbody>
</table>
| Re-authorization criteria | Unless noted otherwise for specific drugs under the medical necessity criteria future re-authorization of the drugs listed may be approved up to 12 months when documentation of ALL of the following are provided:  
  - Continued clinical benefit (i.e., at goal LDL-C or goal TG values specific to the patient)  
  AND  
  - For patients taking Juxtapid® (lomitapide), Nexletol™ (bempedoic acid), Nexlizet™ (bempedoic acid and ezetimibe), Praluent® (alirocumab), or Repatha® (evolocumab) the patient continues to receive the maximum tolerated dose of a statin while receiving therapy |

## Documentation Requirements

The patient’s medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

- Office visit notes that contain the diagnosis, relevant history, physical evaluation, lipid panels, and medication history
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 (e.g., 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 (e.g., 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 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>
</tbody>
</table>

- Atorvastatin (40†)–80 mg
- Rosuvastatin 20 (40) mg
- Atorvastatin 10 (20 ) mg
- Rosuvastatin (5 ) 10 mg
- Simvastatin 20–40 mg‡
- Pravastatin 40 (80 ) mg
- Lovastatin 40 mg
- Fluvastatin XL 80 mg
- Fluvastatin 40 mg BID
- Pitavastatin 2–4 mg
- Simvastatin 10 mg
- Pravastatin 10–20 mg
- Lovastatin 20 mg
- Fluvastatin 20–40 mg
- Pitavastatin 1 mg

### Praluent® and Repatha®

Praluent® (alirocumab) and Repatha® (evolocumab) are proprotein convertase 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 - Praluent® and Repatha®

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 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 - Praluent® and Repatha®**

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 - Praluent® and Repatha®

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.

**Vascepa®**

Vascepa® (icosapent ethyl) forms an active metabolite, eicosapentaenoic acid (EPA), which is subsequently absorbed in the small intestine. Studies suggest that EPA reduces hepatic very-low-density lipoprotein cholesterol (VLDL-C) and triglyceride synthesis and/or secretion as well as increases triglyceride clearance from circulating VLDL particles. Although the exact mechanism of action is unknown, potential mechanisms include increased beta-oxidation, acyl-CoA:1,2-diacylglycerol acyltransferase (DGAT) inhibition, decreased hepatic lipogenesis, and increased plasma lipoprotein lipase activity.

**Efficacy - Vascepa®**

MARINE study was a multicenter, randomized, double-blinded, placebo-controlled Phase III study that was conducted in subjects globally. The population of interest was adult patients with severe hypertriglyceridemia (HTG) with fasting triglyceride (TG) levels ≥500 and ≤2000 mg/dL. The study was conducted over 12 weeks after a 4 - 6 week lead-in period to washout patients of previous lipid-altering or statin therapy followed by a 2-3 week qualifying period that measured fasting TG level. Subjects of this study included men and women > 18 years old that were willing to maintain a stable diet and physical activity throughout the study. Patients (n=610) were screened and the 229 patients that qualified for the study were randomized into 3 treatment
groups: AMR101 4 g/day (n=77), AMR101 2g/day (n= 76), and placebo (n=76). Some subjects from each group discontinued the study: 3, 6, and 5, respectively. The primary endpoint of this study was the placebo-corrected median percent change in TG from baseline to week 12 in both treatment groups. The secondary and exploratory endpoints evaluated the percent change from baseline of the following variables: very-low-density lipoprotein cholesterol (VLDL-C), apolipoprotein B (Apo B), phospholipase A2 (Lp-PLA₂), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), VLDL-TG, and non-HDL-C.

AMR101 showed superiority in efficacy in:

- 4g/day treatment group:
  - significant median percent reduction from baseline in TG, VLDL-C, Apo B, Lp-PLA₂, and non-HDL-C levels by 33%, 29%, 9%, 14%, and 18%, respectively, compared to that of the placebo group (P<0.01)
  - significant median percent reduction in TG levels in patients with >750 mg/dL compared to that of the placebo group
  - significant additive TG lowering effect in patients on concurrent statin therapy by 65%
  - lack of increase in LDL-C levels

- 2g/day treatment group:
  - significant median percent reduction from baseline in the placebo-corrected TG levels by 20% and compared to that of the placebo group (P<0.01)
  - no significant effect on the change from baseline in HDL-C levels
  - significant additive TG lowering effect in patients on concurrent statin therapy by 41%
  - lack of increase in LDL-C levels

ANCHOR was a phase III, multicenter, placebo-controlled, double-blinded, randomized 12-week clinical trial. The population of interest was adult patients at high risk for CVD. Entry criteria includes TG-qualifying values. Eligible patients were randomized to AMR101 4g/day, AMR101 2g/day, or placebo. The Primary endpoint was median placebo-adjusted percent change in TG levels from baseline to week 12. Secondary endpoints were prespecified and included median placebo-adjusted percent change in TC, HDL-C, LDL-C, apo B, VLDL, and Lp-PLA₂.

AMR101 showed superiority in efficacy in:
• 4g/day treatment group:
  o significant median percent reduction vs placebo from baseline in primary endpoint TG by -21.5%.
  o significant median percent reduction vs placebo from baseline in secondary endpoints LDL, non-HDL, VLDL, Lipoprotein associated phospholipase A2, and Apo B by levels of -6.2%, -13.6%, -24.4%, -19.0%, -9.3%, respectively.

• 2g/day treatment group:
  o significant median percent reduction vs placebo from baseline in primary endpoint TG by -10.1%.
  o significant median percent reduction vs placebo from baseline in secondary endpoints LDL-C, non-HDL-C, VLDL, Lp-PLA2, and ApoB by levels of -3.6%, -5.5%, -10.5%, -8.0%, -3.8%, respectively.

REDUCE-IT was a randomized, double-blinded, placebo-controlled Phase III study conducted on subjects globally. The population of interest was adults ≥45 years with established CVD or age ≥50 years with DM and 1 added CV risk factor. Additional inclusion criteria were: fasting LDL-C levels >40 and ≤ 100 mg/dL, and fasting TG levels ≥135 and <500 mg/dL (*2013 amendment fasting TG levels ≥200 and < 500 mg/dL). The study was event-driven and continued until 1,612 primary endpoint events had occurred. The median follow up duration was 58 months (4.9 years). The sample size was based on a hazard ratio assumption of 0.85 with 90% power and a 1-sided α-level of 2.5% to produce a target sample size of 7,990. Patients (n=8,129) were randomized and followed with ITT analysis. Subjects were randomized into treatment (n= 4,089) or placebo (n=4040) group with a 1:1 ratio. The primary outcome of the study was a composite of CV mortality, nonfatal MI, nonfatal stroke, coronary revascularization, and UA. Additional secondary, tertiary, and exploratory outcomes included incidence of CV events, lipid and lipoprotein levels and subgroup analyses.

Icosapent ethyl showed superiority in efficacy in:

• 4g/day treatment group:
  o 25% risk reduction versus placebo in 5-point MACE
  o 26% risk reduction versus placebo in 3-point MACE
  o significant reductions in TG and LDL-C levels
Safety - Vascepa®

In the ANCHOR and MARINE study, reported adverse events for AMR101 4g, AMR101 2g, and placebo were comparable. In the REDUCE-IT study, reported adverse events for icosapent ethyl and placebo were also comparable. Most treatment adverse events were mild or moderate in severity and deemed unrelated to the study drug. The most common treatment-emergent adverse events were gastrointestinal disorders, which also occurred at a larger percentage in the placebo group. Due to the similarity of incidence in adverse effects of icosapent ethyl and placebo, we conclude that icosapent ethyl has an adequate safety profile. Although adverse effects did occur, they were similar to the placebo group.

In the ANCHOR study, a total of 18 SAE were reported. Seven patients in AMR101 4g group, 6 in AMR101 2g, and 5 in the placebo group. In the MARINE study, 2 SAEs occurred, including coronary artery disease in AMR101 4g group and noncardiac chest pain in AMR101 2g group. The most frequently occurring AE in the REDUCE-IT study was pneumonia, with higher incidence in the placebo group (2.6% in icosapent ethyl versus 2.9% in placebo). The incidence of serious TEAE was comparable between placebo and icosapent ethyl (30.7% placebo versus 30.6% icosapent ethyl). However, neither SAE was determined to be correlated to treatment drug.

Nexletol™ and Nexlizet™

Nexletol™ (bempedoic acid) is a first-in-class oral prodrug that inhibits ATP-citrate lyase (ACL). Bempedoic acid is activated to its active metabolite in the liver by bempedoyl-CoA. ACL acts upstream of HMG-CoA reductase in the cholesterol biosynthesis pathway. Inhibiting ACL leads to upregulation of LDL receptors and increase LDL cholesterol clearance without activation in the skeletal muscle.

Efficacy - Nexletol™ and Nexlizet™

Four phase III trials assessed the efficacy and safety of bempedoic acid with a 2:1 randomization of bempedoic acid 180 mg to placebo. The Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen (CLEAR) Harmony and Wisdom recruited patients with high CV risk with either diagnosed ASCVD and/or HeFH whose LDL levels are not adequately controlled on other lipid modifying therapies including statins. CLEAR Serenity recruited patients with a history of intolerance of at least two statins, but who are currently taking other lipid modifying therapies.
CLEAR Tranquility looked at patients with a history of statin intolerance who are currently taking ezetimibe and possibly other lipid modifying therapies.

Although CLEAR Harmony patients have a history of ASCVD and/or HeFH, the mean (±SD) LDL cholesterol level at baseline was only slightly high at 103.2 ± 29.4 mg/dL. Patients were followed for 52 weeks with lipid panels done at week 4, 8, 12, 24, 36 and 52. Results from CLEAR Harmony indicate that when added to maximally tolerated statins, bempedoic acid shows statistically significant reduction in secondary endpoints of LDL cholesterol, non-HDL cholesterol, total cholesterol, ApoB, and hsCRP at week 12. There was also favorable lipid lowering effects for these endpoints up to 52 weeks, but the favorable lipid effects were greatest at week 12 for all endpoints.

- At week 12, bempedoic acid reduced the mean LDL cholesterol level by 19.2 mg/dL. This meant a placebo corrected least-squares (LS) mean difference of -18.1% (95% CI, -20.0 to -16.1; P <0.001) when comparing bempedoic acid to placebo.

- At week 12, the placebo corrected LS mean difference for bempedoic acid follows:
  - Non-HDL cholesterol levels: -13.3% (95% CI, -15.1 to -11.6; P <0.001)
  - Total cholesterol levels: -11.1% (95% CI, -12.5 to -9.8; P <0.001)
  - ApoB levels: -11.9% (95% CI, -13.6 to -10.2; P <0.001)
  - hCRP levels: -21.5% (95% CI, -27.0 to -16.0; P <0.001)

- At week 12, there was no statistically significant placebo corrected LS mean difference in LDL cholesterol levels for patients on a low/moderate statin compared to a high intensity statin (P= 0.18):
  - Patients on low/moderate intensity statin : -20.0% (95% CI, -22.8 to -17.3)
  - Patients on high intensity statin -17.5% (95% CI, -20.2 to -14.7)

CLEAR Wisdom patients have a history of ASCVD and/or HeFH with current hyperlipidemia despite current statin usage. The mean (±SD) LDL cholesterol level at baseline was 120.4 ± 37.9 mg/dL. Patients were followed for 52 weeks with lipid panels done at week 4, 12, 24, and 52. Results from CLEAR Wisdom indicate that when added to the maximally tolerated statins, bempedoic acid shows statistically significant reduction in the primary endpoint of LDL cholesterol at week 12 and in secondary endpoints of non-HDL cholesterol, total cholesterol, ApoB, and hsCRP at week 12 and LDL cholesterol at week 24.
• At week 12, bempedoic acid reduced the mean LDL cholesterol level by 22.8 mg/dL. This meant a placebo corrected LS mean difference of -17.4% (95% CI, -21.0 to -13.9; P <0.001) when comparing bempedoic acid to placebo.

• At week 12, the placebo corrected LS mean difference for bempedoic acid follows:
  o Non-HDL cholesterol levels: -13.0% (95% CI, -16.3 to -9.8; P <0.001)
  o Total cholesterol levels: -11.2% (95% CI, -13.6 to -8.8; P <0.001)
  o ApoB levels: -13.0% (95% CI, -16.1 to -9.9; P <0.001)
  o hCRP levels -8.7% (95% CI, -17.2 to -0.4; P= 0.04)

• At week 24, the placebo corrected LS mean difference for bempedoic acid follows:
  o LDL cholesterol levels: -14.8% (95% CI, -19.5 to -10.0; P <0.001)

CLEAR Serenity patients have a history of intolerance to at least two statins and still require additional lipid-lowering for primary or secondary prevention of CV events. The mean (±SD) LDL cholesterol level at baseline was 157.6 ± 39.9 mg/dL. Patients were followed for 24 weeks with lipid panels done at week 4, 12, and 24. Many patients (58.%) were not receiving any concomitant lipid-modifying therapy, while one-third of patients were on non-statin therapy (the most common agents were ezetimibe and fish oil). Results from CLEAR Serenity indicate that bempedoic acid shows statistically significant reduction in the primary endpoint of LDL cholesterol at week 12 and secondary endpoints of non-HDL cholesterol, total cholesterol, ApoB, and hsCRP at week 12 and LDL cholesterol at week 24.

• At week 12, bempedoic acid reduced the mean LDL cholesterol level by 39.3 mg/dL. This meant a placebo corrected LS mean difference of -21.4% (95% CI, -25.1 to -17.7; P <0.001) when comparing bempedoic acid to placebo.

• At week 12, the placebo corrected LS mean difference for bempedoic acid follows:
  o Non-HDL cholesterol levels: -17.9% (95% CI, -21.1 to -14.8; P <0.001)
  o Total cholesterol levels: -14.8% (95% CI, -17.3 to -12.2; P <0.001)
  o ApoB levels: -15.0% (95% CI, -18.1 to -11.9; P <0.001)
  o hCRP levels -24.3% (95% CI, -35.9 to -12.7; P <0.001)

• At week 24, the placebo corrected LS mean difference for bempedoic acid follows:
CLEAR Tranquility patients have a history of statin intolerance and currently are on ezetimibe 10 mg daily, but still require additional LDL cholesterol lowering therapies. 57.6% of patients had a baseline LDL cholesterol less than 130 mg/dL. Patients were followed for 12 weeks with lipid panels done at week 4, 8, and 12. Results from CLEAR Tranquility indicate that bempedoic acid shows statistically significant reduction in the primary endpoint of LDL cholesterol at week 12 and secondary endpoints of non-HDL cholesterol, total cholesterol, ApoB, and hsCRP at week 12.

- At week 12, the placebo corrected mean difference of LDL cholesterol was -28.5% (95% CI, -34.4 to -25.5; P < 0.001) when comparing bempedoic acid to placebo.
- At week 12, the placebo corrected LS mean difference for bempedoic acid follows:
  - Non-HDL cholesterol levels: -23.6% (95% CI, -26.4 to -20.8; P <0.001)
  - Total cholesterol levels: -18.0% (95% CI, -20.0 to -16.0; P <0.001)
  - ApoB levels: -19.3% (95% CI, -21.6 to -17.0; P <0.001)
  - hsCRP levels -34.6% (P <0.001)

**Safety - Nexletol™ and Nexlizet™**

Bempedoic acid was generally well tolerated with three treatment related non-fatal SAEs compared to placebo. Urinary tract infection, hyperuricemia and hypertension incidence rates were higher in the bempedoic acid group compared to placebo. Safety data is limited to two RCTs that assessed adverse events up to 52 weeks, one RCT with a time horizon of 24 weeks, and one RCT with a time horizon of 12 weeks. The most common adverse events for bempedoic acid (incidence greater than 4%) include nasopharyngitis, myalgia, arthralgia, dizziness, muscle spasms, diarrhea, hyperuricemia, and headache, which occurred in similar incidence rates as the placebo groups. Muscular disorders, gout, urinary tract infection, hypertension, and liver function test increases were reported more frequently in the bempedoic acid group than in the placebo group.

In CLEAR Harmony, SAEs occurred in 216 (14.5%) of 1487 bempedoic acid treated patients (including 13 deaths) and in 104 (14.0%) of 742 placebo treated patients (including 2 deaths). All 15 deaths were judged by the trial site investigator to not be related to study treatment.
In CLEAR Wisdom, SAEs occurred in 106 (20.3%) of 522 bempedoic acid treated patients (including 6 fatal treatment-emergent AE) and in 48 (18.7%) of 257 placebo treated patients (including 2 fatal treatment-emergent AE). All fatal treatment emergent adverse events were found to be unrelated to study drug. Three non-fatal SAEs that occurred were considered to be at least possibly related to study treatment: ulcerative colitis and ischemic stroke in bempedoic acid group and upper abdominal pain in the placebo group.

In CLEAR Serenity, SAEs occurred in 14 (6.0%) of 234 bempedoic acid treated patients and in 4 (3.6%) of 111 placebo treated patients, none of which were considered by the investigator to be related to study treatment.

In CLEAR Tranquility, SAEs occurred in 5 (2.8%) of 181 bempedoic acid treated patients and in 3 (3.4%) of 87 placebo treated patients, none of which were considered by the investigator to be related to study treatment. No fatal SAEs occurred during the study.

Livalo® (pitavastatin)

Many studies have assessed efficacy of Livalo® (pitavastatin) in reducing LDL-C, and influencing lipid parameters and reducing cardiovascular risk, especially to assess pitavastatin versus other HMG-CoA reductase inhibitors. Although head to head studies are still lacking, a meta-analyses reported that pitavastatin has similar cumulative probability of reducing the risk of CHD mortality as rosuvastatin and all-cause mortality as atorvastatin and simvastatin. Specific data in Japanese patients are available. Although pitavastatin shares the same side effects as other agents in its class, there is evidence of fewer drug interactions than some others, due to its being mainly metabolized through glucuronidation. Pitavastatin is available by brand only, suggesting a higher cost over all the other commonly used agents within the same class. There is no evidence of clinical superiority in the majority of patients.

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.
2019 Update

Reviewed Praluent® (alirocumab) and Repatha® (evolocumab) prescribing information and conducted a literature search from July 1, 2018, through August 15, 2019. No new evidence was found that would change this policy.

References


16. This policy was approved by the Pharmacy and Therapeutics Committee September 3, 2015.


<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>9/14/15</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 &quot;effect of alirocumab or evolovumab on cardiovascular morbidity and mortality has not been determined&quot; was removed.</td>
</tr>
<tr>
<td>04/01/19</td>
<td>Interim Review, approved March 12, 2019. Updated and simplified diagnostic criteria for familial hypercholesterolemia, changed LDL-c target from 100mg/dL to 70, removed CK testing requirement for myalgia and eliminated specialty prescribing requirement. Approved by P&amp;T February 26, 2019.</td>
</tr>
<tr>
<td>10/01/19</td>
<td>Annual Review, approved September 5, 2019. Updated criteria to only require maximum tolerated doses of atorvastatin or rosuvastatin. Added peripheral arterial disease and stable or unstable angina as qualifying conditions for ASCVD.</td>
</tr>
<tr>
<td>04/01/20</td>
<td>Interim Review, approved March 10, 2020. Renamed policy from &quot;Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) Inhibitors&quot; to &quot;Pharmacologic Treatment of High Cholesterol&quot;. Added criteria for Vascepa (icosapent ethyl) for established cardiovascular disease and severe hypertriglyceridemia. Added criteria for Nexletol (bempedoic acid) and Nexlizet (bempedoic acid and ezetimibe) for treatment of familial hypercholesterolemia and ASCVD. Moved Ezallor Sprinkle (rosuvastatin), Flolipid (simvastatin liquid), Livalo (pitavastatin), Nikita (pitavastatin), and Zypitamag (pitavastatin) from policy 5.01.605 with identical coverage criteria.</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
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</tr>
<tr>
<td>05/01/20</td>
<td>Interim Review, approved April 14, 2020. Moved Juxtapid (lomitapide) from policy 5.01.605. Kynamro has been withdrawn from the market and no criteria were added to policy for Kynamro. Added criteria to Juxtapid for homozygous familial hypercholesterolemia with requirement to try Praluent or Repatha first. Added criteria for brand simvastatin oral suspension with same criteria as Flolipid. Updated Vascepa (icosapent ethyl) criteria with a daily dose requirement.</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). ©2020 Premera All Rights Reserved.

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• Provides free language services to people whose primary language is not English, such as:
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  - Information written in other languages

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Toll free 855-332-4535, Fax 425-918-5592. TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

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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 S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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中文 (Chinese):

本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知內可能有重要日期。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):


Appelez le 800-722-1471 (TTY: 800-842-5357).

Kreyòl ayisyen (Creole):

Avi silica a gen Enfòmasyon Enpòtan ladann. Avi silica a kapab genyen enfòmasyon enpòtan konsèn aplan aksapak yon las oswa konsèn kouvèt konsèn aplan lan atraav Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi silica a. Ou ka gen pou pran kék aksap avan sèten dat limit pou ka krebte kouvèt asirants sante w la oswa pou yo ka ede w avèk depans yo. Se dwa w pou resevwa enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rate nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):


Hmoob (Hmong):


Ilokano (Illocano):

Daytoy a Pakdaak ket naglaoon iti Napateg nga Impormasion. Daytoy a pakdaak mabalin nga adja ket naglaoon iti napateg nga impormasion maipanggep iti aplikasyonony weno coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a pelta iti daytoy a pakdaak. Mabalin nga adja rumbeng nga aramideny nga adja sakkay dagiti partikular a naituding nga adjawarna a tapo tapa mapagtalainedyo ti coverage ti salun-atyo weno tulong kadagiti gastos. Adda karbenganyo a mangala ti daytoy nga impormasion ken tulong iti bukodyo a pagasao nga awan ti bayadangon. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):

Questo avviso contiene informazioni importanti. Questo avviso può contenere informazioni importanti sulla tua domanda o copertura attraverso Premera Blue Cross. Potrebbero esserci date chiave in questo avviso. Potrebbe essere necessario un tuo intervento entro una scadenza determinata per consentirti di mantenere la tua copertura o sovvenzione. Hai il diritto di ottenere queste informazioni e assistenza nella tua lingua gratuitamente.

Chiama 800-722-1471 (TTY: 800-842-5357).
Premera Blue Cross 800-722-1471 (TTY: 800-842-5357)