Cigna Drug and Biologic Coverage Policy

Effective Date .......................... 01/15/2018
Next Review Date .................... 01/15/2019
Coverage Policy Number .......... 1509

Subject  PCSK9 Inhibitors

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Coverage Policy

PCSK9 Inhibitors include:

- Praluent® (alirocumab)
- Repatha® (evolocumab)

NOTE: Receipt of sample product does not satisfy any criteria requirements for coverage.

Cigna covers alirocumab (Praluent) or evolocumab (Repatha) as medically necessary for the treatment of hyperlipidemia in an adult (18 years or older) when ALL of the following criteria are met:

- Individual has documentation of EITHER of the following:
  - Established clinical atherosclerotic cardiovascular disease (ASCVD) as evidenced by any of the following:
    - Coronary heart disease (acute coronary syndromes, history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization)
    - Cerebrovascular disease (stroke, transient ischemic attack)
    - Peripheral arterial disease (PAD) of atherosclerotic origin
  - Heterozygous Familial Hypercholesterolemia (HeFH) as defined by one of the following:
    - WHO Criteria (Dutch Lipid Network clinical criteria, score greater than 8; see Appendix 1)
    - Simon-Broome Criteria (definite HeFH, see Appendix 2)
    - Confirmed genetic testing
- ONE of the following:
  - Documented contraindication per FDA label to statin therapy
Documented intolerance to at least TWO statins with symptoms or abnormal lab results being temporally related to statin and other causes being ruled out
Inadequate response (LDL-C greater than 70 mg/dL if ASCVD present or LDL-C greater than 100 mg/dL if there is no documentation of ASCVD) when ALL of the following criteria are met:
- Lipid lowering therapy with statins defined as EITHER of the following:
  - **High-intensity statin therapy** (atorvastatin 40-80 mg/day or rosuvastatin 20-40 mg/day)
  - **Moderate intensity, or low intensity statin therapy** and documented intolerance to atorvastatin 40-80 mg/day or rosuvastatin 20-40 mg/day
- Statin therapy is used in combination with ezetimibe (Zetia) OR there is a contraindication per FDA label, documented intolerance, or the individual is not a candidate for ezetimibe (for example, LDL-C lowering to achieve target exceeds 15-20%)
- Regimen has been taken for a minimum duration of 12 consecutive weeks with demonstrated adherence (80% or greater proportion of days covered [PDC] for current lipid lowering therapy regimen)

- **Use is adjunctive to diet and maximally tolerated statin therapy (if not contraindicated or intolerant)**

**Initial approval duration is 6 months.**
- For Repatha, the dose approved for ASCVD/HeFH is 140 mg every 2 weeks OR 420 mg monthly via Repatha Pushtronex.
- For Praluent, the recommended starting dose of Praluent is 75 mg once every 2 weeks. An alternative starting dosage is 300 mg once every 4 weeks. For patients receiving Praluent 75 mg every 2 weeks, the dosage may be adjusted to the maximum dosage of 150 mg administered every 2 weeks. For patients receiving Praluent 300 mg every 4 weeks, the dosage may be adjusted to 150 mg every 2 weeks starting the new dose on the next scheduled dosing date.

**Reauthorization for 12 months requires ALL of the following:**
- Documented evidence of clinical beneficial response (for example, demonstrated reduction of LDL-C)
- PCSK9 inhibitor is used in combination with maximally tolerated statin therapy (if not contraindicated or intolerant)
- Documented adherence measure at 80% or greater PDC (Proportion of Days Covered) for PCSK9 inhibitor and statin therapy (if not contraindicated or intolerant)

Cigna covers evolocumab (Repatha) as medically necessary for the treatment of homozygous familial hypercholesterolemia (HoFH) in an individual 13 years of age or older when ALL of the following criteria are met:
- **Documented diagnosis of HoFH as demonstrated by EITHER of the following:**
  - Genetic confirmation of 2 mutant alleles at the LDL receptor, ApoB, PCSK9 or ARH adaptor protein gene locus
  - An untreated LDL-C greater than 500 mg/dL OR a total treated LDL-C greater than or equal to 300 mg/dL AND one of the following:
    - Cutaneous or tendinous xanthoma before the age of 10 years
    - Untreated LDL-C levels consistent with heterozygous familial hypercholesterolemia in both parents (greater than 190 mg/dL)
- **Inadequate response (LDL-C greater than 70 mg/dL if ASCVD present or LDL-C greater than 100 mg/dL if there is no documentation of ASCVD) with maximally tolerated lipid lowering therapy regimen (for example, high-intensity statin, ezetimibe, LDL apheresis) AND use will be adjunctive to diet and maximally tolerated lipid lowering therapy (if not contraindicated or intolerant)
- **Will not be used in combination with lomitapide (Juxtapid®) or mipomersen (Kynamro®)**
Initial approval duration is 6 months. The dose of Repatha approved for HoFH is 420 mg once monthly.

Reauthorization for 12 months requires ALL of the following:
  o Documented evidence of clinical beneficial response (for example, demonstrated reduction of LDL-C)
  o PCSK9 inhibitor is used in combination with maximally tolerated lipid lowering therapy (if not contraindicated or intolerant)
  o Documented adherence measure at 80% or greater PDC (Proportion of Days Covered), for PCSK9 inhibitor and maximally tolerated lipid lowering therapy (if not contraindicated or intolerant)

Cigna does not cover the use of PCSK9 Inhibitors for any other indication including the following because it is considered experimental, investigational or unproven (this list may not be all-inclusive):
  - Cigna does not cover PCSK9 inhibitors for individuals with 2 null LDLR pathogenic variants and/or LDL receptor activity less than 2%.

When coverage is available and medically necessary, the dosage, frequency, and duration of therapy should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to PCSK9 Inhibitors.

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA Approved Indications</th>
</tr>
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</table>
| Praluent (alirocumab) | Primary Hyperlipidemia  
Praluent is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C.  

Limitations of Use  
The effect of Praluent on cardiovascular morbidity and mortality has not been determined. |
| Repatha (evolocumab) | Prevention of Cardiovascular Events  
In adults with established cardiovascular disease, Repatha is indicated to reduce the risk of myocardial infarction, stroke, and coronary revascularization.  

Primary Hyperlipidemia (Including Heterozygous Familial Hypercholesterolemia)  
Repatha is indicated as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for the treatment of adults with primary hyperlipidemia to reduce low-density lipoprotein cholesterol (LDL-C).  

Homozogous Familial Hypercholesterolemia  
Repatha is indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) for the treatment of patients with homozogous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C. |

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA Recommended Dosing</th>
</tr>
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</table>
| Praluent (alirocumab) | The recommended starting dose of Praluent is 75 mg once every 2 weeks administered subcutaneously, since the majority of patients achieve sufficient LDL-C reduction with this dosage. An alternative starting dosage for patients who prefer less frequent dosing is 300 mg once every 4 weeks (monthly).  
For patients receiving Praluent 75 mg every 2 weeks, measure LDL-C levels within 4 to 8 weeks of initiating Praluent. If the LDL-C response is inadequate, the dosage may be adjusted to the maximum dosage of 150 mg administered every 2 weeks. Reassess LDL-C within 4 to 8 weeks. |
For patients receiving Praluent 300 mg every 4 weeks, measure LDL-C just prior to the next scheduled dose, since in some patients LDL-C can vary considerably between doses with this regimen. If LDL-C reduction is inadequate, the dosage may be adjusted to 150 mg every 2 weeks, starting the new dose on the next scheduled dosing date. Reassess LDL-C within 4 to 8 weeks.

If an every-2-week dose is missed, instruct the patient to administer the injection within 7 days from the missed dose and then resume the patient’s original schedule. If the missed dose is not administered within 7 days, instruct the patient to wait until the next dose on the original schedule.

If an every-4-week dose is missed, instruct the patient to administer the injection within 7 days from the missed dose and then resume the patient’s original schedule. If the missed dose is not administered within 7 days, instruct the patient to administer the dose, starting a new schedule based on this date.

Repatha (evolocumab) The recommended subcutaneous dosage of Repatha in patients with HeFH or patients with primary hyperlipidemia with established clinical atherosclerotic CVD is either 140 mg every 2 weeks OR 420 mg once monthly. When switching dosage regimens, administer the first dose of the new regimen on the next scheduled date of the prior regimen.

The recommended subcutaneous dosage of Repatha in patients with HoFH is 420 mg once monthly. In patients with HoFH, measure LDL-C levels 4 to 8 weeks after starting Repatha, since response to therapy will depend on the degree of LDL-receptor function.

If an every 2 week or once monthly dose is missed, instruct the patient to:
- Administer Repatha as soon as possible if there are more than 7 days until the next scheduled dose, or,
- Omit the missed dose and administer the next dose according to the original schedule.

**Drug Availability**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Praluent (alirocumab)</td>
<td>Available for injection as single-dose pre-filled pens or syringes as 75 mg/mL or 150 mg/mL in packages of 1 pen or syringe or 2 pens or syringes.</td>
</tr>
<tr>
<td>Repatha (evolocumab)</td>
<td>Available for injection as a 140 mg/mL solution in a single-use prefilled syringe or SureClick® autoinjector in packages of 1 syringe or 1, 2, or 3 SureClick® autoinjectors. Also available as 420 mg/3.5 mL solution in a single-use Pushtronex™ system (on-body infusor with prefilled cartridge).</td>
</tr>
</tbody>
</table>

**General Background**

**Disease Overview**

Elevated low-density lipoprotein cholesterol (LDL-C) is the primary target for treatment of hyperlipidemia as it is a major risk factor for coronary heart disease. The National Health and Nutrition Examination Survey (NHANES) data from 2005-2008 estimate that 71 million (33.5%) of U.S. adults (20 years of age and older) have a high LDL-C. NHANES data also indicates that only 48.1% were treated and 33.2% achieved LDL-C control (CDC, 2011). Familial hypercholesterolemia (FH) is characterized by very high LDL-C levels and early ASCVD (Jacobson, 2015). The incidence of homozygous FH is estimated as 1 in 1,000,000 and the incidence of heterozygous FH is estimated as 1 in 500 (Cuchel, 2014).

Lifestyle modifications (e.g., diet, exercise) are non-pharmacologic therapies for hyperlipidemia. Randomized clinical trials utilizing 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors or statin therapy have demonstrated reduction in atherosclerotic cardiovascular disease (ASCVD) events in primary and secondary prevention (Stone, 2013).

The long-term persistence with statin therapy was addressed in a retrospective cohort study of over 34,000 individuals 65 years and older enrolled in a state Medicaid and pharmaceutical assistance programs. The
proportion of days covered (PDC) was calculated based on the quantity dispensed and the number of days supplied from each prescription. A PDC of at least 80% was considered “adherent” to therapy. For the first 3 months of treatment, the PDC was 79%. At 6 months, the PDC dropped to 56% and was 50% after 12 months and 42% after 120 months. The authors concluded that persistence with statin treatment decreases over time with the greatest decline occurring during the first 6 months of therapy (Benner, 2002).

Pharmacology
PCSK9 (proprotein convertase subtilisin kexin type 9) leads to the degradation of low-density lipoprotein receptors (LDLR) in the liver. Inhibition of PCSK9 results in an increased number of LDLR to remove LDL, resulting in lower LDL-C levels.

Guidelines
Clinical practice guidelines recommend statins as the primary treatment modality for hyperlipidemia when LDL-C lowering therapy is indicated.

- **American College of Cardiology/American Heart Association (ACC/AHA)**
The ACC/AHA guideline for the treatment of blood cholesterol in adults is focused on primary and secondary atherosclerotic cardiovascular disease (ASCVD) risk reduction and establishes 4 groups that would benefit from statin therapy. As a result, the goal of treatment is the intensity of statin therapy (refer to Table 1) as opposed to treating to a target LDL-C (Stone, 2013).

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

The first statin benefit group includes individuals with established ASCVD (defined as acute coronary syndromes, a 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) and recommends high-intensity statin therapy for individuals 75 years of age and younger (moderate-intensity statin therapy for individuals older than 75 years, when high-intensity is contraindicated, or presence of individual characteristics predisposing to statin-associated adverse events). The second statin benefit group includes individuals 21 years of age and older with an LDL-C greater than or equal to 190 mg/dL for primary prevention. High-intensity statin therapy is recommended and intensifying statin therapy (including adding nonstatin drug) to achieve at least a 50% LDL-C reduction is advised. The third statin benefit group is primary prevention in adults with diabetes with a recommendation of either moderate-intensity or high-intensity statin therapy for those at higher ASCVD risk based on the Pooled Cohort Equation (ASCVD risk calculator). The final statin benefit group includes primary prevention in adults without diabetes and an LDL-C of 70-189 mg/dL with statin therapy recommendations based on ASCVD risk as determined by the Pooled Cohort Equation (Stone, 2013).

For monitoring statin response, ACC/AHA recommends regularly assessing adherence to medication, as well as therapeutic response to statin therapy. Fasting lipid panels should be performed within 4-12 weeks after initiation or dose adjustment, and every 3-12 months thereafter (Stone, 2013). The guidelines note that LDL-C levels and percent reduction should be used to assess response to therapy and adherence. In addition, the maximally tolerated statin intensity is recommended for individuals who are candidates for high- or moderate-intensity statin therapy and cannot tolerate it (Stone, 2013).
The ACC authored an expert consensus decision pathway to address the gap of evidence in the use of non-statin therapy in ASCVD. Ezetimibe should be considered for most individuals as the first non-statin medication, however, either ezetimibe or PCSK9 inhibitors may be considered for patients with ASCVD with comorbidities. PCSK9 inhibitors are also a treatment option for high risk individuals with familial hypercholesterolemia who do not reach their therapy goals on maximally tolerated statin therapy and ezetimibe (Lloyd-Jones, 2017).

The AHA published a scientific statement on familial hypercholesterolemia and recommends commencing treatment based on LDL-C levels. In pediatric patients, treatment options provided include statins (except pitavastatin), cholestyramine, colesevelam, ezetimibe, and ezetimibe/simvastatin. For adults with HeFH, the initial goal is to reduce LDL-C by 50% through use of a high-intensity statin. If LDL-C remains above goal after 3 months of adherence to therapy and individual’s LDL-C remains above 100 mg/dL (no CAD or major risk factors) or 70 mg/dL (with CAD or other major risk factors), use two-drug therapy with atorvastatin or rosuvastatin and ezetimibe. If LDL-C remains above goal after 3 months of adherence to therapy, consider a three-drug combination (one option being a PCSK9 inhibitor). For HoFH, treatment options include statins, ezetimibe, mipomersen, lomitapide, PCSK9 inhibitors, and lipid apheresis (Gidding, 2015).

- **European Atherosclerosis Society (EAS)**
  A position paper from the EAS Consensus Panel on Familial Hypercholesterolaemia provides diagnostic criteria for homozygous familial hypercholesterolemia (HoFH). Diagnosis is made either genetically or clinically.
  - Genetic confirmation of two mutant alleles at the LDLR, APOB, PCSK9, or LDLRAP1 gene locus OR
  - An untreated LDL-C >13 mmol/L (500 mg/dL) or treated LDL-C ≥ 8 mmol/L (300 mg/dL)* together with either:
    - Cutaneous or tendon xanthoma before age 10 years or
    - Untreated elevated LDL-C levels consistent with heterozygous FH in both parents
  * These LDL-C levels are only indicative, and lower levels, especially in children or in treated patients, do not exclude HoFH

The panel also provides a suggested algorithm for the management of HoFH and recommends LDL-C targets of less than 100 mg/dL (< 2.5 mmol/L) for adults; less than 135 mg/dL (< 3.5 mmol/L) for children; and less than 70 mg/dL (< 1.8 mmol/L) if clinical cardiovascular disease. Management strategies include a combination of statin therapy (at highest dose depending on tolerability) with or without ezetimibe and LDL-apheresis every 1 or 2 weeks. The panel also notes that lomitapide and mipomersen are available as adjunctive treatments. PCSK9 inhibitors are mentioned as future therapeutic options (Cuchel, 2014).

- **National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)**
  The NCEP ATP III guidelines focus on LDL-C as the primary target of therapy and establishes risk categories by counting major risk factors (cigarette smoking, hypertension, low HDL-C, family history of premature coronary heart disease [CHD], and age) and estimating the 10-year risk of CHD (NCEP, 2002).

  Individuals with established CHD or CHD risk equivalents (other clinical forms of atherosclerotic disease [peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease], diabetes, multiple risk factors that confer a 10-year risk for CHD greater than 20%) have an LDL-C goal less than 100 mg/dL (NCEP, 2002). A 2004 update provides a therapeutic option goal LDL-C of less than 70 mg/dL when the risk is very high (established cardiovascular disease with either multiple major risk factors, severe and poorly controlled risk factors, or multiple risk factors of the metabolic syndrome). (Grundy, 2004) Patients with 2 or more risk factors (an estimated 10-year risk of CHD of 20% or less) have an LDL-C goal of less than 130 mg/dL and those with zero or 1 risk factor (an estimated 10-year risk of CHD of less than 10%) have an LDL-C goal of less than 160 mg/dL (NCEP, 2002).

  For primary prevention, NCEP ATP III recommends initiating LDL-lowering drug therapy with a statin, bile acid sequestrant, or nicotinic acid. If the LDL-C goal is not met after 6 weeks, the LDL-C lowering therapy should be intensified by considering a higher dose of statin, adding a bile acid sequestrant or nicotinic acid. If the LDL-C goal is not achieved in another 6 weeks, the drug therapy should be intensified or the patient referred to a lipid specialist. Once the LDL-C goal is met, the patient should be monitored for response and adherence to therapy every 4 to 6 months (NCEP, 2002).
The NLA recommends statin therapy as the primary modality to lower ASCVD risk. The guidelines provide criteria to ascertain an individual’s risk for ASCVD (low, moderate, high, very high) and assigns an LDL-C treatment target based on the risk category. Major risk factors for ASCVD include age, family history of early coronary heart disease, current cigarette smoking, hypertension, and low HDL-C (Jacobson, 2015).

Individuals at very high risk include those with established ASCVD and those with diabetes mellitus type 1 or 2 and at least 2 other major ASCVD risk factors or evidence of end-organ damage. The NLA sets the LDL-C treatment goal for very high risk patients at less than 70 mg/dL. Individuals at high risk include those with at least 3 major ASCVD risk factors, diabetes mellitus type 1 or 2, chronic kidney disease (stage 3B or 4), baseline LDL-C of 190 mg/dL or more (e.g., familial hypercholesterolemia), or a quantitative risk score reaching the high-risk threshold. The LDL-C treatment goal for those at high risk is less than 100 mg/dL. For those with familial hypercholesterolemia, the guidelines note that even lower LDL-C levels may be considered for those with multiple or poorly controlled other major ASCVD risk factors (Jacobson, 2015).

The NLA recommends initiating therapy with a statin, unless contraindicated, and intensifying therapy or referring to a lipid specialist if goals are not met. Once goals are achieved, response and adherence to therapy should be monitored every 4 to 12 months (Jacobson, 2015). PCSK9 inhibitor therapy may be considered to further reduce LDL-C in selected very-high-risk patients who meet the definition of statin intolerance (Orringer, 2017). Statin intolerance may be characterized by an inability to tolerate at least two statins (one statin at a low starting daily dose and another statin at any daily dose), either objectionable symptoms or abnormal lab results temporally related to statin treatment, and reversible when statin discontinued, but reproducible by rechallenge with other known causes being excluded (Bays, 2016).

Clinical Efficacy

• Alirocumab (Praluent)
The efficacy and safety of alirocumab demonstrated in 5 clinical trials was used to support its use in the treatment of primary hyperlipidemia in ASCVD and HeFH. ODYSSEY LONG TERM enrolled adults (n = 2,341) with HeFH (diagnosed either through genotyping or clinical criteria [definite FH with Simon Broome or WHO/Dutch Lipid Network criteria] or with established coronary heart disease (CHD) or a CHD risk equivalent with an LDL-C of 70 mg/dL or greater. All subjects were receiving either high-dose statin or maximally tolerated statin (with or without other lipid lowering therapy) and were randomized to alirocumab 150 mg every 2 weeks or placebo. Alirocumab-treated patients had a 61% reduction in LDL-C from baseline to week 24 (Robinson, 2015). ODYSSEY-COMBO I enrolled adults with either an LDL-C 70 mg/dL or greater and established cardiovascular disease or an LDL-C 100 mg/dL or greater and CHD risk equivalents. A total of 316 patients were enrolled and randomized to either alirocumab 75 mg every 2 weeks (with titration to 150 mg every 2 weeks based on LDL-C levels) or placebo. All patients were continued on maximally tolerated statin therapy with or without other lipid lowering therapy. Alirocumab produced a 48% reduction in LDL-C from baseline to week 24 (Kereiakes, 2015).

The other 3 clinical trials (ODYSSEY FH I, FH II, and HIGH FH) used to support FDA approval of alirocumab enrolled individuals with HeFH (diagnosed by genotyping or clinical criteria) on maximally tolerated statin with or without other lipid lowering therapy. ODYSSEY FH I and II randomized patients to either alirocumab 75 mg every 2 weeks (with titration to 150 mg every 2 weeks based on LDL-C levels) or placebo. Alirocumab produced a 57.9% reduction in LDL-C in FH I and a 51.4% reduction in FH II from baseline to week 24 and maintained these reductions to week 78 (Kastelein, 2015). ODYSSEY HIGH-FH is unpublished and enrolled individuals with a baseline LDL-C of at least 160 mg/dL and randomized to either alirocumab 150 mg every 2 weeks or placebo. The mean percent change from baseline to week 24 in LDL-C was -43% with alirocumab (Sanofi-Aventis U.S. LLC, 2015).

• Evolocumab (Repatha)
The safety and efficacy of evolocumab supporting its FDA approval was established in 4 pivotal trials. LAPLACE-2 included individuals with primary hypercholesterolemia and mixed dyslipidemia who had a specified LDL-C level based on the presence and intensity of statin therapy. A total of 1,899 patients were enrolled and the FDA evaluated a subset of 296 patients with ASCVD. Evolocumab 420 mg once monthly or 140 mg every 2 weeks were compared to placebo and all patients were stabilized on a baseline statin regimen. The primary endpoint evaluated percent change from baseline LDL-C to week 12 and was -58% for the monthly regimen and
-67% for the every 2 week evolocumab regimen (Amgen, 2015; Robinson, 2014). DESCARTES enrolled adults with a baseline LDL-C of at least 75 mg/dL. Approximately 900 patients were enrolled and the FDA evaluated 139 patients with ASCVD. Evolocumab 420 mg once monthly was compared to placebo as add-on therapy to background lipid-lowering treatment. Evolocumab decreased LDL-C from baseline to week 52 by 52% (Amgen, 2015; Blom, 2014).

RUTHERFORD-2 enrolled adults who met the Simon-Broome clinical criteria for heterozygous familial hypercholesterolemia (HeFH) who were on stable lipid lowering therapy. A total of 329 patients were randomized to evolocumab 420 mg monthly, evolocumab 140 mg every 2 weeks, or placebo. At week 12 LDL-C reduced by 61% in the evolocumab every 2 weeks group and 56% in the evolocumab monthly group (Raal, 2015b). TESLA-B included patients 12 years of age and older (13 years of age and older enrolled) with homozygous FH (HoFH) diagnosed either genetically or clinically. Exclusion criteria included use of mipomersen or lomitapide within the previous 5 months and lipoprotein apheresis within 8 weeks. All patients in the trial were on statin therapy and 92% were on ezetimibe. Evolocumab 420 mg once monthly lowered LDL-C 23% from baseline to week 12 (Raal, 2015a).

FOURIER was a randomized, double-blind, placebo-controlled, multinational clinical trial from February 2013 through June 2015. A total of 27,564 patients with atherosclerotic cardiovascular disease and LDL-C levels >/= 70 mg/dL while on statin therapy were randomized to either evolocumab 140 mg every 2 weeks or 420 mg every month, or placebo. Evolocumab or placebo were added to an optimized lipid lowering therapy regimen (including a statin) in patients with a history of atherosclerotic cardiovascular disease with an additional risk factor and an LDL-C of at least 70 mg/dL and followed for a median of 26 months. Evolocumab reduced the primary endpoint (a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization): evolocumab 9.8% and placebo 11.3% (HR 0.85; p < 0.001). No differences in cardiovascular death or death from any cause. No significant differences in overall rates of adverse events, serious adverse events, or adverse events thought to be related to the study agent and leading to discontinuation of the study regimen. There were more injection site reactions with evolocumab vs. placebo (2.1% vs. 1.6%) (Sabatine, 2017).

Experimental, Investigational, or Unproven Uses
PCSK9 inhibitors work by preventing PCSK9 from binding to the LDLR receptor, which leads to receptor breakdown. With PCSK9 inhibition, the LDLR receptor can be recycled to the liver for further use to decrease LDL levels. This requires a functional LDL receptor to be effective. Therefore, homozygous or compound heterozygous LDLR genetics null mutations are not recommended for PCSK9 therapy as the medication is not effective without a functional LDLR gene (Baum, 2017).

APPENDIX 1 – WHO Criteria (Dutch Lipid Network Clinical Criteria) for Diagnosis of Heterozygous Familial Hypercholesterolemia (HeFH) (Nordestgaard, 2013)

<table>
<thead>
<tr>
<th>Diagnostic Scoring for Heterozygous Familial Hypercholesterolemia</th>
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<tbody>
<tr>
<td><strong>Family History</strong></td>
</tr>
<tr>
<td>First degree relative with known premature (men &lt; 55 yrs, women &lt; 60 yrs) coronary vascular disease</td>
</tr>
<tr>
<td>First degree relative with known LDL-cholesterol &gt;95th percentile for age and sex and/or First degree relative with tendon xanthomata and/or arcus cornealis</td>
</tr>
<tr>
<td>Children below 18 yrs with LDL-cholesterol &gt;95th percentile for age and sex</td>
</tr>
<tr>
<td><strong>Clinical History</strong></td>
</tr>
<tr>
<td>Patient has premature (men &lt; 55 yrs, women &lt; 60 yrs) coronary artery disease</td>
</tr>
<tr>
<td>Patient has premature (men &lt; 55 yrs, women &lt; 60 yrs) cerebral or peripheral vascular disease</td>
</tr>
<tr>
<td><strong>Physical Examination</strong></td>
</tr>
<tr>
<td>Tendon xanthomata</td>
</tr>
<tr>
<td>Arcus cornealis below the age of 45 yrs</td>
</tr>
</tbody>
</table>
Laboratory Analysis

<table>
<thead>
<tr>
<th></th>
<th>mmol/L</th>
<th>mg/dL</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-cholesterol</td>
<td>&gt; 8.5</td>
<td>&gt; 330</td>
<td>8</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>6.5 – 8.4</td>
<td>250 – 329</td>
<td>5</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>5.0 – 6.4</td>
<td>190 – 249</td>
<td>3</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>4.0 – 4.9</td>
<td>155 – 189</td>
<td>1</td>
</tr>
</tbody>
</table>

(HDL-cholesterol and triglycerides are normal)

DNA Analysis

Functional mutation low-density lipoprotein receptor gene present | 6

Diagnosis of HeFH is:

| Certain When | > 8 points |
| Probable When | 6-8 points |
| Possible When | 3-5 points |

APPENDIX 2 – Simon Broome Register Diagnostic Criteria for Heterozygous Familial Hypercholesterolemia (HeFH) (Scientific Steering Committee, 1991)

Definite familial hypercholesterolemia is defined as:
- Total cholesterol > 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years or total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult. (Levels either pre-treatment or highest on treatment)
- PLUS
  - Tendon xanthomas in patient or in 1st degree relative (parent, sibling, child), or in 2nd degree relative (grandparent, uncle, aunt)
- OR
  - DNA-based evidence of an LDL receptor mutation or familial defective apo B-100

Possible familial hypercholesterolemia is defined as:
- Total cholesterol > 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years or total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult. (Levels either pre-treatment or highest on treatment)
- And at least one of the following:
  - Family history of myocardial infarction below 50 years of age in 2nd degree relative or below 60 years of age in 1st degree relative.
  - Family history of raised cholesterol > 7.5 mmol/L (290 mg/dL) in adult 1st or 2nd degree relative or > 6.7 mmol/L (260 mg/dL) in child or sibling under 16 years of age.

Coding/Billing Information

Note: PCSK9 Inhibitors are typically covered under pharmacy benefit plans. Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed. Medical drug coding and diagnosis codes, however, are generally not required for pharmacy claims submissions, therefore, this section is not in use.

References


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