**Medication Policy Manual**

**Topic:** Repatha™, evolocumab

**Date of Origin:** July 10, 2015

**Committee Approval Date:** July 14, 2017

**Next Review Date:** July 2018

**Effective Date:** August 1, 2017

**IMPORTANT REMINDER**

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

**Description**

Evolocumab (Repatha) is a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor indicated as an adjunct to diet and maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C). It also indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C. The effect of evolocumab (Repatha) on cardiovascular morbidity and mortality has not been determined.
I. Most contracts require prior authorization approval of evolocumab (Repatha). Evolocumab (Repatha) may be considered medically necessary when criteria A, B, or C below are met.

A. A diagnosis of **heterozygous familial hypercholesterolemia (HeFH)** when all of criteria 1 through 3 below are met.

1. The diagnosis has been established by or in conjunction with a specialist in cardiology or lipid management and there is clinical documentation of at least one of the following a, b, or c:
   a. A definitive diagnosis of FH using Simon Broome diagnostic criteria or Dutch Lipid Clinic Network criteria (see appendix 1 and 2).
   
   OR
   
   b. An untreated lo-density lipoprotein cholesterol of ≥ 190 mg/dL (or ≥ 160 mg/dL in patients less than 20 years of age) with at least one of the following:
      
      (1). Physical signs of FH, such as presence of tendon xanthomas, premature corneal arcus, tuberous xanthomas, or xanthelasma.
      
      OR
      
      (2). Family History of FH.
      
      OR
      
   c. Presence of a causal mutation for FH by DNA testing (e.g. a mutation in the *LDLR, APOB, PCSK9,* or *LDLRAP1* genes).

   AND

2. All of criteria a and b below are met:
   a. Treatment with maximally tolerated statin therapy has been ineffective, contraindicated, or not tolerated.

   **Statin intolerance is defined as the inability to tolerate, due to muscle symptoms, at least three different statin medications at the lowest FDA-approved starting dose when other potential causes of muscle symptoms have been maximally managed or ruled out (see appendices 3 and 4).**

   See appendix 5 for a list of statin contraindications.

   AND

   b. Treatment with ezetimibe (Zetia) has been ineffective, contraindicated, or not tolerated.

3. Treatment with maximally tolerated lipid lowering therapy has failed to achieve an LDL-C of less than or equal to 100 mg/dL after at least 12 weeks of therapy.
OR
B. A diagnosis of homozgyous familial hypercholesterolemia (HoFH) when criteria 1 and 2 below are met:

1. The diagnosis has been established by or in conjunction with a specialist in cardiology or lipid management and there is clinical documentation of at least one of the following:
   a. Genetic confirmation of two mutant alleles at the LDLR, APOB, PCSK9, or LDLRAP1 gene locus.

2. An untreated low-density lipoprotein cholesterol (LDL-C) of > 500 mg/dL (or a treated LDL-C of > 300 mg/dL) with either:
   (1). Cutaneous or tendon xanthoma before age 10 years
   OR
   (2). Evidence of heterozygous familial hypercholesterolemia in both parents.

OR
C. A diagnosis of clinical atherosclerotic cardiovascular disease (ASCVD) when all of criteria 1 through 3 below are met (see appendix 6 for definitions of ASCVD).

1. Evolocumab (Repatha) has been prescribed by or in conjunction with a specialist in cardiology or lipid management.

AND

2. Criteria a and b below are met:
   a. Treatment with maximally tolerated statin therapy has been ineffective, contraindicated, or not tolerated.

A statin is considered ineffective if patients are not able to tolerate high-intensity dose levels (see appendix 7) or have not had an LDL-C reduction of at least 50% while on a high-intensity statin for at least 12 weeks.

Statin intolerance is defined as the inability to tolerate, due to muscle symptoms, at least three different statin medications at the lowest FDA-approved starting dose and other potential causes of muscle symptoms have been maximally managed or ruled out (see appendices 3 and 4).

See appendix 5 for a list of statin contraindications.

AND

b. Treatment with ezetimibe has been ineffective, contraindicated, or not tolerated.
AND
3. Treatment with maximally tolerated lipid lowering therapy has failed to achieve an LDL-C of less than or equal to 100 mg/dL after at least 12 weeks of therapy.

II. Administration, Quantity Limitations, Authorization Period
A. OmedaRx considers evolocumab (Repatha) to be a self-administered medication.
B. When prior authorization is approved, evolocumab (Repatha) may be covered in quantities of 140 mg every other week or 420 mg once monthly.
C. Authorization shall be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

III. Evolocumab (Repatha) is considered not medically necessary when used for:
A. Non-familial hyperlipidemia/hypercholesterolemia
B. Primary prevention of atherosclerotic cardiovascular disease (ASCVD)
C. Primary prevention of ASCVD in patients who are statin-intolerant

IV. Evolocumab (Repatha) is considered investigational when used for all other conditions, including but not limited to:
A. In combination with any other PCSK9 inhibitor, lomitapide (Juxtapid), or mipomersen (Kynamro).

Position Statement
- Evolocumab (Repatha) is a subcutaneous proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C). It is also indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.
- American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines define clinical ASCVD as acute coronary syndromes, a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin.
- ACC/AHA Guidelines recommend high-intensity statins for high-risk patients, such as those with clinical ASCVD or with HeFH. On average, high-intensity statins lower LDL-C by approximately ≥50%.
- Evolocumab (Repatha) has been studied in multiple placebo- or active-controlled phase 3 studies which included a variety of patients including those with HeFH and/or clinical ASCVD. Evolocumab (Repatha) has also been studied in patients with HoFH.
One outcomes study has been completed in patients with ASCVD. While treatment with evolocumab (Repatha) reduced the composite endpoint of CV death, MI, stroke, hospitalization for unstable angina, and coronary revascularization, the magnitude of benefit was small.

Clinical guidelines have not been updated to include the results of the evolocumab (Repatha) outcomes study. Additional guidance is needed to clarify the role in therapy of evolocumab (Repatha), the ideal patient population, and goals of therapy (i.e. target LDL levels or target doses).

Due to the small magnitude of benefit and lack of updated clinical guidelines, use of evolocumab (Repatha) in ASCVD is limited to high-risk patients who are statin intolerant or have not had the expected response to statin therapy.

Statins have been proven to reduce cardiovascular events and mortality, thus they are the preferred treatment to reduce the risk ASCVD and recommended as the first-line treatment by multiple guidelines.

HeFH and HoFH may be diagnosed via clinical criteria, such as baseline LDL values, family history, and physical manifestations of FH, or through genetic testing. Commonly used diagnostic criteria include Simon Broome Diagnostic Criteria and Dutch Lipid Clinic Network Criteria for Heterozygous FH Diagnosis.

Based on results from the IMPROVE-IT study, ezetimibe has also been shown to modestly reduce cardiovascular events. Although, it was studied in a very narrow, high-risk population it is a treatment option in patients with clinical ASCVD or HeFH.

A 2016 ACC Expert Consensus Decision Pathway on non-statin therapies concluded that non-statins could be considered in patients who do not have an anticipated response to statins (defined as a ≥50% reduction in LDL-C or an LDL-C of less than 100 mg/dL). The consensus committee supported ezetimibe 10 mg daily as the first-line non-statin and a bile acid sequestrant as a second-line non-statin. If these measures do not achieve the anticipated response a PCSK9 inhibitor may be considered.

Statins are also recommended as initial therapy for the treatment of HeFH. Non-statins may be considered in patients who are unable to reach target LDL-levels or who are statin intolerant. Although ACA/AHA guidelines do provide treatment recommendations for patients with HeFH, guidelines specifically for HeFH have been produced by the National Lipid Association (NLA) and European Atherosclerosis Society (EAS).

NLA treatment guidelines for HeFH recommend targeting a 50% reduction in LDL-C from baseline; however higher risk patients may require a more aggressive treatment goal of less than 100 mg/dL. Patients will generally require treatment with multiple agents to achieve LDL-C goals.

Statin-intolerance is not well defined. In a clinical trial of alirocumab (Praluent) in statin intolerant patients (defined as the inability to tolerate due to muscle symptoms at least two statins with at least one at the lower FDA-approved starting dose), over 70% of patients who were randomized to receive blinded atorvastatin 20 mg were able to complete the study. Although, this trial was conducted in a “statin intolerant” population, the majority of these patients were able to tolerate statin therapy, thus requiring trials of multiple statins prior to coverage of a PCSK9 inhibitor is warranted.
Furthermore, a consensus statement by the EAS generally recommends trials of different three statins before alternatives are considered.

- Evolocumab (Repatha) is administered subcutaneously. The recommended starting dose for evolocumab (Repatha) is 140 mg once every two weeks or 420 mg once monthly. Monthly dosing offers similar efficacy to biweekly dosing.
- The recommend starting dose for patients with HoFH is 420 mg administered subcutaneously once monthly.
- Evolocumab (Repatha) has not been studied in combination with any other PCSK9 inhibitor, lomitapide (Juxtapid®), or mipomersen (Kynamro™).
- Evolocumab (Repatha) appears to be well tolerated, but there is limited long-term safety experience. Safety considerations of special interest include the effects of prolonged periods of very low LDL-C values (e.g. less than 25 mg/dL) and the effect of evolocumab (Repatha) on neurocognitive events. There were no concerning signals in the FOURIER study but additional long-term studies and clinical experience will help to further clarify the safety profile.

**Background**

**HoFH**
- HoFH is a rare, genetic disease characterized by abnormally elevated LDL cholesterol levels and an increased risk for early onset coronary heart disease. LDL levels can range from 300 to over 1000 mg/dL. If not treated, affected patients often die in early adulthood. [1]
- Treatment options include evolocumab (Repatha), lomitapide (Juxtapid), mipomersen (Kynamro), traditional lipid-lowering medications, and LDL-apheresis. [1]

**Clinical Efficacy**
- The FOURIER study evaluated the impact of evolocumab on cardiovascular outcomes in patients with clinical ASCVD. The primary endpoint was the composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. Patients were randomized to either evolocumab (Repatha) or placebo and all patients were on background high or moderate intensity statin therapy.[2]
  * After a median follow-up of 26 months, evolocumab modestly reduced the risk of the primary endpoint compared to placebo (9.8% vs. 11.3%, respectively; hazard ratio, 0.85; 95% CI, 0.79 to 0.92; P<0.001).
  * Evolocumab also significantly reduced the risk of the key secondary composite of CV death, MI, or stroke compared to placebo (5.9% vs. 7.4%, respectively; hazard ratio, 0.80; 95% CI, 0.73 to 0.88; P<0.001). However, results for cardiovascular mortality alone were not statistically significant.
- The body of evidence supports that evolocumab (Repatha) produces substantial reductions in LDL-C. [3]
* The primary endpoint in the majority of evolocumab (Repatha) phase 3 studies was percent change in LDL-C. Reductions in LDL-C ranged from 54% to 71% in patients in patients with clinical ASCVD or HeFH. [3]

* In patients with HoFH the mean LDL-C reduction was approximately 31%. [4]

- Several outcomes trials have demonstrated that statins reduce the risks of cardiovascular and cerebrovascular events. [5]

- Reduction in cardiovascular and cerebrovascular risk is not unique to any specific statin and has been demonstrated with many of the available statins in a variety of patient populations, such as in patients with coronary heart disease, high cholesterol levels, normal cholesterol levels, hypertension, diabetes and previous stroke. [6]

**Guidelines**

**HeFH**

- NLA treatment guidelines for HeFH recommend targeting a 50% reduction in LDL-C from baseline; however higher risk patients may require a more aggressive treatment goal of less than 100 mg/dL. High risk HeFH patients included those with clinically evident CHD or other atherosclerotic cardiovascular disease, diabetes, a family history of very early CHD (in men < 45 years of age and women < 55 years of age), current smoking, two or more CHD risk factors, or high lipoprotein (a) ≥ 50 mg/dL. Intensification of therapy may also be considered in patients without any of the listed previously factors, if LDL-C remains ≥ 160 mg/dL (or non-HDL cholesterol ≥ 190 mg/dL), or if an initial 50% decrease is LDL-C is not achieved. [6]

- Although treatment targets are recommend by clinical guidelines, they are based primarily on surrogate endpoints, expert opinion, and studies in patients without familial hypercholesterolemia. [6-8]

- NLA guidelines recommend statins as the initial treatment for all patients with FH. Ezetimibe, niacin, and bile acid sequestrants are considered reasonable treatment options for intensification of therapy, or for those intolerant of statins. EAS guidelines for HeFH provide generally similar treatment recommendations, but recommend different target LDL levels. [6]

**ASCVD**

- Clinical guideline have not been updated to incorporate the results of the FOURIER study. While evolocumab has been shown to modestly reduce the risk of cardiovascular events compared to placebo, its place in therapy is not well defined. Due to the modest benefit, additional guidance on the ideal population and goals are treatment are needed.

- The 2013 American College of Cardiology and American Heart Association (ACC/AHA) treatment guidelines recommend statins for certain risk groups. The guidelines recommend treating to a target statin dose based on risk (e.g. high intensity statins for high-risk groups), rather the treating to a target LDL-C value. The guidelines also state that non-statins do not provide acceptable ASCVD risk reduction benefits relative to their potential for adverse effects in the routine prevention of ASCVD. [5]
ACC/AHA guidelines recommend statins as the primary treatment for to reduce ASCVD, non-statins have not been shown to reduce ASCVD events. The guideline panel could find no studies supporting the routine use of non-statin drugs alone or combined with statin therapy to reduce further ASCVD events. Furthermore, identification of any RCTs that assessed ASCVD outcomes in statin-intolerant patients was not found. [5,9]

ACC/AHA guidelines also state that LDL–C levels and percent reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards. [6]

2014 National Lipid Association (NLA) guidelines provide similar recommendations but recommend treating to target LDL-C levels instead of target statin doses. In contrast to ACC/AHA guidelines, NLA guidelines support the use of combined statin and non-statin therapy in patients who have not attained their goal cholesterol levels after the maximum tolerated statin dosage has been reached and for those who have contraindications or are intolerant to statin therapy.

A 2016 ACC Expert Consensus Decision Pathway on non-statin therapies affirmed that high-intensity statins are the mainstay of therapy for patients with ASCVD. The committee also reinforced that LDL-C thresholds are factors to be considered but are not definitive triggers for intensification of lipid modifying therapy. The anticipated response to high-intensity statin therapy is a ≥50% reduction in LDL-C, although a target of 100 mg/dL could be considered as most patients in clinical trials of high-intensity statins achieved an LDL of less than 100 mg/dL. In patients with a less-than anticipated response the panel concluded that additional therapies are warranted. The consensus committee supported ezetimibe (Zetia) 10 mg daily as the first-line non-statin and a bile acid sequestrant as a second-line non-statin. If these measures do not achieve the anticipated response a PCSK9 inhibitor may be considered. The panel stated that if a PCSK9 inhibitor was initiated it should be continued along with maximally tolerated statin therapy. [10]

**Statin intolerance**

GUASS-3 was a two phase, crossover study designed to evaluate the use of evolocumab (Repatha) in patients with statin intolerance. In phase A, a 24-week crossover procedure with atorvastatin 20 mg or placebo was used to identify patients who had muscle symptoms while on atorvastatin but not placebo. Patients who completed phase A entered into phase B where they underwent a two-week washout period before being randomized to ezetimibe (Zetia) or evolocumab (Repatha) for 24 weeks. [11]

* In phase A, muscle symptoms occurred in 209 of 491 patients (42.6%) while taking atorvastatin but not while taking placebo. Of these patients 199 were then enrolled into phase B.

* In phase B, muscle symptoms were reported in 28.8% of patients who received ezetimibe (Zetia) and 20.7% of patients who received evolocumab (Repatha). Reductions in LDL-C were significantly greater in the evolocumab (Repatha) group.
While evolocumab (Repatha) demonstrated efficacy in statin intolerant patients, the high percentage of patients who experienced muscle symptoms while on placebo highlight the need for proper identification of patients who are unequivocally statin intolerant.

ODYSSSEY ALTERNATIVE was a 24-week study of alirocumab (Praluent) in patients who were considered to be statin intolerant, which was defined as inability to tolerate at least two statins due to muscle symptoms, with one at the lowest FDA-approved dose. \[12,13\]

- Muscle related symptoms must have begun or increased during statin therapy and stopped when statin therapy was discontinued.
- The trial included a 4-week, single-blind placebo run-in period, patients who experienced muscle symptoms during the placebo run-in period were excluded. After completion of the run-in period patients were randomized to alirocumab (Praluent), ezetimibe (Zetia), or atorvastatin.
- In total, 314 of 361 patients completed the placebo run-in period. Of the 47 placebo run-in failures, 23 (48.9%) reported at least one skeletal muscle-related adverse event.
- Approximately 70% of patients randomized to atorvastatin completed 24 weeks of the double-blind treatment period. The intent of this arm was to rechallenge patients with a statin.
- Fewer patients experienced skeletal muscle-related TEAEs in the alirocumab group than the atorvastatin (HR: 0.61; 95% CI: 0.38 to 0.99) or ezetimibe (HR: 0.70; 95% CI: 0.47 to 1.06) groups. Fewer patients in the alirocumab (Praluent) group discontinued the study due to musculoskeletal AEs compared to the atorvastatin group (15.9% versus 22.2%, respectively).
- Although, this trial was conducted in a “statin intolerant” population, the majority of these patients were able to tolerate statin therapy, thus requiring multiple statin-rechallenges prior to use of a PCSK9 inhibitor is warranted.

Other studies have also concluded that most patients can tolerate a statin after being rechallenged.

- In a retrospective analysis of 1,605 statin-intolerant patients conducted by researchers at the Cleveland Clinic, 72.5% of patients were able to tolerate a statin after re-challenge. \[14\]
- Authors of a separate retrospective analysis conducted at two academic medical centers concluded that most patients who are rechallenged can tolerate statins long-term. In this study, 92.2% of patients who were re-challenged with a statin were able to continue taking statins after 12-months.

The EAS recommends a structured work-up to identify individuals with clinically relevant statin-associated muscle symptoms generally to at least three different statins, so that they can be offered therapeutic regimens to satisfactorily address their cardiovascular risk. \[15,16\]
The ACC has developed an online application to help providers assess, treat, and manage patients with possible statin intolerance. The tool is available at: http://tools.acc.org/StatinIntolerance/

**Safety**

- Evolocumab (Repatha) is generally well tolerated with a favorable safety profile. Common adverse events in clinical trials included nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions. [3]

- Evolocumab (Repatha) contains a warning for allergic reactions [3]

- All marketed statin-containing medications have safety records that are consistent for the statin class. [17]
  * Rhabdomyolysis is a rare side-effect of all statins (0.1%).
  * Hepatotoxicity occurs rarely (less than 1%) with statins.
  * Increases in HbA1c and fasting serum glucose levels have been reported with all statins.

- Ezetimibe is generally well tolerated. [18]

**Dosing considerations**

- Evolocumab (Repatha) is administered as a subcutaneous injection in the abdomen, thigh, or upper arm. It is currently available as 140 mg/mL prefilled syringes or auto-injectors. [3]

- The recommended starting dose of evolocumab (Repatha) for patients with HeFH or clinical ASCVD is 140 mg once every 2 weeks or 420 mg once monthly. The recommended starting dose for patients with HoFH is 420 mg once monthly. [3]

<table>
<thead>
<tr>
<th>Appendix 1: Dutch Lipid Clinic Network criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Criteria</strong></td>
</tr>
<tr>
<td><strong>Group 1: family history</strong></td>
</tr>
<tr>
<td>First-degree relative with known premature (less than age 55 for males or 65 for females) coronary heart disease</td>
</tr>
<tr>
<td>* First-degree relative with known LDL cholesterol above 95(^{th}) percentile</td>
</tr>
<tr>
<td>* First-degree relative with tendon xanthoma and/or corneal Arcus</td>
</tr>
<tr>
<td>First-degree relative with tendon xanthoma and/or corneal Arcus</td>
</tr>
<tr>
<td>* Children &lt; 18 years with LDL cholesterol above 95(^{th}) percentile</td>
</tr>
<tr>
<td><strong>Group 2: clinical history</strong></td>
</tr>
<tr>
<td>Premature coronary heart disease</td>
</tr>
<tr>
<td>Subject has cerebral or peripheral vascular disease</td>
</tr>
<tr>
<td><strong>Group 3: physical examination</strong></td>
</tr>
<tr>
<td>(i) Tendon xanthoma</td>
</tr>
</tbody>
</table>

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### Appendix 1: Dutch Lipid Clinic Network criteria

<table>
<thead>
<tr>
<th>(ii) Corneal arcus in a person before age 45</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 4: biochemical results (LDL-C)</strong></td>
<td></td>
</tr>
<tr>
<td>&gt;8.5 mmol/L (325 mg/dL)</td>
<td>8</td>
</tr>
<tr>
<td>5–8.4 mmol/L (251–325 mg/dL)</td>
<td>5</td>
</tr>
<tr>
<td>5.0–6.4 mmol/L (191–250 mg/dL)</td>
<td>3</td>
</tr>
<tr>
<td>4.0–4.9 mmol/L (155–190 mg/dL)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Group 5: molecular genetic testing (DNA analysis)</strong></td>
<td></td>
</tr>
<tr>
<td>(i) Causative mutation shown in the LDLR, APOB, or PCSK9 genes</td>
<td>8</td>
</tr>
</tbody>
</table>

**Scoring**

- > 8 points: Definite FH
- 6-8 points: Probably FH
- 3-5 points: Possible FH
- <3 points: Unlikely FH

### Appendix 2: Simon Broome Register Diagnostic Criteria for Definitive FH \[19\]

**Adults:** total cholesterol levels > 290 mg/dL (7.5 mmol/L) or LDL-C > 190 mg/dL (4.9 mmol/L)

**Children less than 16 years of age:** Total cholesterol levels > 260 mg/dL (6.7 mmol/L) or LDL-C > 155 mg/dL (4.0 mmol/L)

Plus at least one of the two:

1. Physical findings: tendon xanthomas or tendon xanthomas in a first or second degree relative
   **OR**
2. DNA-based evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation.

### Appendix 3: Risk Factors for Statin-Associated Muscle Symptoms \[5,16\]

- Hypothyroidism
- Multiple or serious co-morbidities, including reduced renal or hepatic function
- Rheumatologic disorders such as polymyalgia rheumatica
- Steroid myopathy
- Vitamin D deficiency
- Primary muscle diseases
- Acute infection
- Organ transplant recipients
### Appendix 3: Risk Factors for Statin-Associated Muscle Symptoms [5,16]

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe trauma</td>
</tr>
<tr>
<td>HIV</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Major Surgery</td>
</tr>
<tr>
<td>History of creatinine kinase elevation</td>
</tr>
<tr>
<td>History of pre-existing/unexplained muscle/joint/tendon pain</td>
</tr>
<tr>
<td>Genetic factors such as polymorphisms in genes encoding cytochrome P450 isoenzymes or drug transporter</td>
</tr>
<tr>
<td>High level of physical activity</td>
</tr>
<tr>
<td>Dietary effects (excessive grapefruit or cranberry juice)</td>
</tr>
<tr>
<td>Excess alcohol</td>
</tr>
<tr>
<td>Drug abuse (cocaine, amphetamines, heroin)</td>
</tr>
</tbody>
</table>

### Appendix 4: Examples of Drug-drug interactions that may increase the risk of skeletal muscle effects with High-Intensity Statins

<table>
<thead>
<tr>
<th>Drug-drug Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong inhibitors of CYP 3A4 (e.g. clarithromycin, itraconazole, protease inhibitors)</td>
</tr>
<tr>
<td>Grapefruit Juice</td>
</tr>
<tr>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Gemfibrozil and other fibrates</td>
</tr>
<tr>
<td>Niacin</td>
</tr>
<tr>
<td>Colchicine</td>
</tr>
</tbody>
</table>

### Appendix 5: Contraindications to Statin Therapy [5,17]

<table>
<thead>
<tr>
<th>Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels</td>
</tr>
<tr>
<td>History of rhabdomyolysis</td>
</tr>
<tr>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Nursing Mothers</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
</tbody>
</table>
### Appendix 6: Clinical Atherosclerotic Cardiovascular Disease (ASCVD) [5]

- Acute coronary syndromes
- History of coronary or other arterial revascularization
- History of myocardial infarction
- History of stable or unstable angina
- History of stroke or transient ischemic attack (TIA)
- Peripheral arterial disease presumed to be of atherosclerotic origin

### Appendix 7: Statin Comparison Chart [5]

<table>
<thead>
<tr>
<th>% LDL-C Lowering</th>
<th>Statin Name</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low-intensity:</strong> &lt; 30%</td>
<td>fluvastatin</td>
<td>20 mg, 40 mg</td>
</tr>
<tr>
<td></td>
<td>lovastatin</td>
<td>10 mg, 20 mg</td>
</tr>
<tr>
<td></td>
<td>lovastatin ER (Altoprev®)</td>
<td>20 mg</td>
</tr>
<tr>
<td></td>
<td>pitavastatin (Livalo®)</td>
<td>1 mg</td>
</tr>
<tr>
<td></td>
<td>pravastatin</td>
<td>10 mg, 20 mg</td>
</tr>
<tr>
<td></td>
<td>simvastatin</td>
<td>5 mg, 10 mg</td>
</tr>
<tr>
<td><strong>Moderate-intensity:</strong> 31% - 49%</td>
<td>atorvastatin</td>
<td>10 mg, 20 mg</td>
</tr>
<tr>
<td></td>
<td>fluvastatin ER (Lescol XL®)</td>
<td>80 mg</td>
</tr>
<tr>
<td></td>
<td>lovastatin</td>
<td>40 mg</td>
</tr>
<tr>
<td></td>
<td>lovastatin ER (Altoprev®)</td>
<td>40 mg, 60 mg</td>
</tr>
<tr>
<td></td>
<td>pitavastatin (Livalo®)</td>
<td>2 mg, 4 mg</td>
</tr>
<tr>
<td></td>
<td>pravastatin</td>
<td>40 mg, 80 mg</td>
</tr>
<tr>
<td></td>
<td>rosuvastatin</td>
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<td>simvastatin</td>
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<td><strong>High-intensity:</strong> ≥ 50%</td>
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Cross References

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<td>Branded Lipid-Modifying Medications, dru336</td>
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<td>Praluent™, alirocumab, dru406</td>
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References


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| 7/14/2017     | • Removed requirement for prior bile acid sequestrant  
• Updated dosing to include 420 mg once monthly in patients with ASCVD. |
| 6/10/2016     | • Rearranged diagnostic criteria for HeFH  
• Removed requirement for prior fibrate  
• Clarified that use in combination with any other PCSK9 inhibitor is considered investigational |