DISCLAIMER

This Medical Policy is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina Clinical Policy (MCP) document and provide the directive for all Medicare members.

SUMMARY OF EVIDENCE/POSITION

This policy addresses the coverage of Praluent (alirocumab) for the heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease (ASCVD) when appropriate criteria are met.

- **PREFERRED:** Statins have been proven to reduce cardiovascular events and mortality, therefore statins are the preferred treatment to reduce the risk ASCVD and recommended as the first-line treatment by multiple guidelines.
  - Based on guidelines from the American College of Cardiology and American Heart Association (ACC/AHA), statins are the standard of care for most patients due to extensive evidence that statins significantly reduce the risk of major coronary heart disease, strokes, revascularizations, and death.
  - The ACC/AHA guidelines emphasize the appropriate intensity of statin therapy to reduce CV risk in patients who will benefit. No statin was specified as the preferred, but instead, statins with related doses are categorized as high-intensity (lowers LDL-C by approximately ≥ 50%), moderate-intensity (lowers LDL-C by approximately 30% to < 50%), and low-intensity (lowers LDL-C by < 30%). Only atorvastatin and Crestor® (rosuvastatin tablets) are categorized as high-intensity statin therapy, which is recommended for many patient populations at high CV risk.
  - ACA/AHA guidelines provide treatment recommendations for patients with HeFH; however guidelines specifically for HeFH have been produced by the National Lipid Association (NLA) and European Atherosclerosis Society (EAS).
  - National Lipid Association (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.
**PREFERRED PCSK9 Inhibitor: Repatha (evolocumab)**

A published meta-analyses\(^1\) concludes the LDL-C lowering effect of the two PCSK9 inhibitors [Repatha (evolocumab) and Praluent (alirocumab)] were similar. Additionally, the lack of head-to-head randomized trials and currently limited data on the two drugs effects on key clinical outcomes, such as stroke, MI, and cardiovascular death does not support the superiority of any PCSK9 inhibitors over the other. Therefore when there is no demonstrated difference in safety or efficacy, the most cost-effective therapy provides the best value for Molina Healthcare members and currently, **Repatha (evolocumab) is the preferred PCSK9 inhibitors for the indications addressed in this policy.**

- Evidence to support treatment to a specific LDL target for reducing CV outcomes is lacking in most populations, including those with HeFH. Therefore, the LDL value that will result in the greatest reduction in CV risk is unknown.
- Both alirocumab and evolocumab have been associated with severe hypersensitivity reactions, patients and caregivers should be informed to seek immediate medical attention if signs and symptoms of an allergic reaction occur.
- Due to the relatively limited safety database (n=3340 exposed to alirocumab; n=5710 exposed to evolocumab) and the lack of long-term safety data for alirocumab or evolocumab, the FDA has required large, long-term, randomized controlled trials to assess the incidence and severity of adverse events associated with these agents including new-onset diabetes, injection site reactions, hypersensitivity reactions, immunogenicity and its consequences and neurologic events.
- Long-term effectiveness or safety data are not presently available for PCSK9 inhibitors. It is unknown if alirocumab will be at least as effective as statins at decreasing cardiovascular morbidity and mortality, however ongoing long-term studies are evaluating this. In the absence of long-term effectiveness data, it is uncertain whether LDL-C reduction with PCSK9 inhibitors produces similar reductions in clinical events compared with statins.
- The effect of alirocumab on cardiovascular (CV) morbidity or mortality is unknown. The ODYSSEY OUTCOMES trial is underway which will enroll 18,000 having an ACS within the past year. The trial will be completed in late 2017.

**Guidelines**

The American Heart Association and American College of Cardiology (ACC/AHA)\(^B\) (2013) AND The National Lipid Association (NLA) guideline do not address the PCSK9 inhibitors at the time of this writing.

**ACC/AHA Guidelines\(^B\)**

The 2013 ACC/AHA cholesterol guidelines no longer recommend specific LDL-C goals for treatment. Instead, the guidelines emphasize lifestyle modifications and treatment with moderate or high intensity statins depending upon a patient’s risk. The 4 risk groups include those with ASCVD, patients with DM, patients with 10 year risk of ASCVD >7.5%, and those with LDL-C > 190mg/dL.

Guidelines for the treatment of hypercholesterolemia were released from the American College of Cardiology/American Heart Association (ACC/AHA) in 2013. **NOTE:** In 2013, as these guidelines were being written and published, there was no evidence of existing non-statin therapies provide acceptable ASCVD risk-reduction benefits\(^B\)

- Statin therapy is recommended for individuals at increased risk of atherosclerotic cardiovascular disease (ASCVD) in whom the potential for ASCVD risk reduction outweighs the potential for adverse effects from statins. Lifestyle modification (i.e., adhering to a heart-healthy diet, exercising regularly, avoiding tobacco products, and maintaining a healthy weight) remains a crucial component of health promotion and ASCVD risk reduction, both before and while using cholesterol-lowering drug therapies.
- The current gold standard of pharmacologic treatment of hypercholesterolemia is the use of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, also known as statins\(^B\).
- Use of statins reduces mortality and myocardial infarction in adults with coronary heart disease and reduces cardiovascular disease and stroke in patients with diabetes or elevated cardiovascular disease risk.
In 2013, ACC/AHA updated their guidelines on treatment of blood cholesterol to emphasize cardiovascular risk rather than LDL cholesterol goals. These guidelines identified 4 major patient groups that benefit from statin therapy:

- Patients with clinical atherosclerotic cardiovascular disease
- Patients with LDL ≥190 mg/dL
- Patients ages 40 to 75 years with diabetes and LDL 70 to 189 mg/dL
- Patients ages 40 to 75 years without diabetes and LDL 70 to 189 mg/dL with an estimated 10-year risk of atherosclerotic cardiovascular disease of ≥7.5%

It is recommended that patients who fit into these categories receive moderate- to high-dose statin therapy.  

The National Lipid Association (NLA) recommends LDL goals, <100 mg/dL for those at high CV risk and <70 mg/dL for those at very high risk.

**CLASSIFICATION: PCSK9 Blocker, Antilipemic Agent**

**FDA INDICATIONS**

**Hyperlipidemia, primary:** Adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-cholesterol (LDL-C).

- Primary heterozygous familial hypercholesterolemia, In combination with a statin
- Primary hypercholesterolemia, Atherosclerotic cardiovascular disease; in combination with a statin

Limitations of use: The effect of alirocumab on cardiovascular morbidity and mortality has not been determined.

**Available as:**
Injection: 75 mg/mL or 150 mg/mL solution in a single-dose pre-filled pen or single-dose pre-filled syringe

**FDA Approved:** July 25, 2015

Black Box Warnings: *None at the time of this writing*
**Recommendations/Coverage Criteria**

Praluent (alirocumab) may be authorized for members who meet ALL of the following criteria [ALL]

1. **Prescriber specialty [ONE]**

   - Prescribed by, or in consultation with, a cardiologist, endocrinologist, or physician lipidologist. Submit consultation notes.
     - Lipidologist defined in ‘Definitions’ section.

2. **Diagnosis/Indication [ONE]**

   Clinical documented diagnosis of (includes clinical notes from the member’s medical records including any applicable labs and/or tests, supporting the diagnosis) ONE (1) of the following FDA approved indications: [ONE]

   - **Heterozygous Familial Hypercholesterolemia (HeFH)** as determined by ONE (1) of the following.a [ONE]
     - Genotype-confirmed: HeFH confirmed by genetic testing. Documentation requireda
       - Genetic testing may provide definitive diagnosis in individuals with mutations in any of the following:
         - low-density lipoprotein receptor gene (LDLR), apolipoprotein B gene (APOB), pro-protein convertase subtilisin/kexin 9 gene (PCSK9)
     - Clinical criteria: HeFH confirmed as “definite” by a score of > 8 using the Dutch Lipid Clinic Network criteria (all points added to calculate the total score must be documented) OR confirmed as “definite” by the Simon-Broome criteria. Clinical evidence and laboratory results must be submitted to support the diagnosis.
       - 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).a

   - **Hyperlipidemia with Clinical Atherosclerotic Cardiovascular Disease (ASCVD)**
     The 2013 ACC/AHA Guidelines define clinical ASCVD as having one or more of the following.b [ONE]
     - Acute coronary syndromes (ACS)
     - History of myocardial infarction (MI)
     - Stable or unstable angina (UA)
     - Coronary or other arterial revascularization procedure (e.g., PTCA, CABG)
     - Stroke or transient ischemic attack (TIA)
     - Peripheral artery disease (PAD)

3. **Age/Gender/Other restrictions [ALL]**

   - 18 years of age or older
     - Safety and efficacy in pediatric patients have not been established.a

   - Secondary causes for dyslipidemia (i.e., diabetes, hypothyroidism, high triglycerides, obstructive liver disease, chronic renal failure, and drugs that increase LDL-C and decrease HDL-C [progestins, anabolic steroids, and corticosteroids]), have been excluded or, if appropriate, treated17. Prescriber submit clinical documentation or labs excluding secondary causes dyslipidemia
4. Step/Conservative Therapy/Other condition Requirements [ALL]

☐ Clinical documentation of a therapeutic failure on, intolerance to, or contraindication to high-intensity statin therapy met by ONE (1) of the following: [A, B, OR C]

A. Adherent* on a maximally tolerated high-intensity statin therapyB (daily dose of atorvastatin 40 to 80 mg or rosuvastatin 20 to 40mg) and Zetia (ezetimibe) 10mg/day. *NOTE: Adherence is defined as at least 85% of the time as confirmed by claims history for at least 180 days OR an attestation from the Prescriber.

- Goal levels should be achieved in approximately 6 months, therefore criterion is for 180 days (6 months) according to NLA algorithm for monitoring and progression of lipid-lowering therapy.6

- Per 2016 ACC Expert Consensus on Role of Non-Statin Therapies for LDL-C Lowering for Management of ASCVD Risk:6
  - ‘Ezetimibe is the first non-statin medication that should be considered in most of the patient scenarios, given its safety and tolerability, as well as demonstrated, though modest, efficacy when added to moderate-dose statin in one trial of patients with acute coronary syndrome.’8
  - Alirocumab and evolocumab may be considered if the goals of therapy have not been achieved on maximally tolerated statin and ezetimibe in higher-risk patients with clinical ASCVD or familial hypercholesterolemia. Given the lack of long-term safety and efficacy data on these agents, they are not recommended for use in primary prevention patients in the absence of familial hypercholesterolemia.8

AND

Inability to achieve and maintain an LDL-C cholesterol level at or below goal (< 100 mg/dL or < 70 mg/dL based on patient risk) with a combination of medications, diet, and exercise by documentation of ONE (1) of the following: [ONE]

☐ LDL-C ≥100 mg/dL for HeFH (evaluated within the last 3 months)

OR

☐ LDL-C ≥ 70 mg/dL for ASCVD OR ASCVD + FH (evaluated within the last 3 months)

NOTE: Confirmed by claims history or an attestation from the Prescriber on behalf of the member if no claims history is available (i.e., if member is newly enrolled to Molina Healthcare)

Note

- The 2004 update of the Adult Treatment Panel (ATP) III of the National Cholesterol Education Program (NCEP) established a target goal of < 100 mg/dL for high-risk patients and an optional target of <70 mg/dL for very high-risk patients (Grundy 2004).
- Refer to Appendix 3 for References/Guidelines supporting criterion goal (< 100 mg/dL or < 70 mg/dL based on patient risk)
- Goal of cholesterol-lowering treatment in adults with familial hypercholesterolemia:6
  - ≥ 50% reduction in low-density lipoprotein cholesterol (LDL-C):6
  - in patients at high risk for cardiovascular disease, more aggressive goals of LDL-C < 100 mg/dL and non-HDL-C < 130 mg/dL may be needed to reduce risk of cardiovascular disease6
- Individuals with HeFH are typically unable to achieve an LDL-C goal of <100 mg/dL despite the use of multiple cholesterol-lowering therapies (Stone 2014). In a study of 1249 patients with HeFH treated in lipid clinics in The Netherlands (of which 96% were on statin therapy), only 21% achieved an LDL level <100 mg/dL. An alternative >50% LDL-C reduction was achieved in 49% of patients (Pijlman 2010).16

☐ Has not achieved a 50% reduction in LDL-C from baseline while on maximally tolerated statin therapyB,3,6

- Goal of cholesterol-lowering treatment in adults with familial hypercholesterolemia:6
  - ≥ 50% reduction in low-density lipoprotein cholesterol (LDL-C):6
  - in patients at high risk for cardiovascular disease, more aggressive goals of LDL-C < 100 mg/dL and non-HDL-C < 130 mg/dL may be needed to reduce risk of cardiovascular disease6

- High intensity statin therapy is anticipated to lower LDL-C levels by approximately ≥50% and moderate intensity statin therapy is anticipated to lower LDL-C levels by approximately 30% to < 50% (2013 ACC/AHA).8 Refer to Appendix 1 for ‘Statin Intensity Chart’ The ACC/AHA guidelines
define high-intensity statin therapy as a daily dosage that lowers LDL cholesterol approximately 50% and can be achieved with atorvastatin 40-80mg per day or rosuvastatin 20-40mg per day.\(^8\)

- Goal levels should be achieved in approximately 6 months, therefore criterion is for 180 days (6 months) according to NLA algorithm for monitoring and progression of lipid-lowering therapy.\(^6\)
- Individuals with HeFH are typically unable to achieve an LDL-C goal of <100 mg/dL despite the use of multiple cholesterol-lowering therapies (Stone 2014).\(^8\) In a study of 1249 patients with HeFH treated in lipid clinics in The Netherlands (of which 96% were on statin therapy), only 21% achieved an LDL level <100 mg/dL. An alternative >50% LDL-C reduction was achieved in 49% of patients (Pijlman 2010).\(^16\)

B. Member has ANY of the following contraindication(s) to statin therapy [ONE]

**NOTE:** Laboratory tests showing evidence of muscle inflammation, alterations of liver function tests from baseline and/or liver damage required.

- Hypersensitivity to statins or any component of the product
- Active liver disease
- CK levels (defined as >10 times the Upper Limit of Normal [ULN])
  - *Myositis or ‘myopathy’ (elevated CK >10 times ULN)*\(^G\)
  - *Rhabdomyolysis is defined as muscle symptoms, very high creatine kinase (10 times ULN), and increased serum creatinine, often with dark urine and myoglobinuria:*\(^G\)
    - *CK level >10 × ULN or >10,000 IU/L accompanied by significant an elevation in serum creatinine or a requirement for IV hydration therapy (National Lipid Association Statin Safety Assessment Task Force, Am J Cardiology 2006)*
- Unexplained persistent elevation of hepatic transaminases (greater than 3 times the upper limit of normal [ULN] occurring on 2 or more occasions)
- Women who are pregnant or may become pregnant
- Breast-feeding

C. If a re-trial of statins is not contraindicated (refer to ‘Contraindication’ criterion below) medical record documentation of **TWO (2) statin re-trials** with switching to an alternate statin [low- or moderate-intensity statin (e.g., simvastatin, pravastatin)], reducing statin dose, every other day statins required.

- Pravastatin and fluvastatin appear to have much less intrinsic muscle toxicity than other statins (see ‘Statin characteristics’ above). In patients who have developed statin myopathy (other than rhabdomyolysis) on a statin other than pravastatin or fluvastatin, an option is to switch to one of those two medications once symptoms have resolved off statin therapy.\(^11\)
- In patients who develop evidence of muscle toxicity while on statin therapy, recommendation is to assess for drug interactions, and if none are noted, we check vitamin D and thyroid function status.\(^11\)
- Daily dosing of statins is preferred whenever possible, since daily regimens are the ones that have been studied and proven to reduce clinical events. Clinical experience suggests that alternate-day dosing may improve the tolerability of statins in patients experiencing myalgias, and this strategy can reasonably be tried in patients unable to tolerate daily statin therapy.\(^11\)

**Per 2016 ACC Expert Consensus on Role of Non-Statin Therapies for LDL-C Lowering for Management of ASCVD Risk:**\(^4\) The approach to suspected statin intolerance should include temporary discontinuation of statin therapy, lower dosing, re-challenge preferably with 2-3 statins of differing metabolic pathways, and intermittent (1-3x weekly) dosing of long half-life statins.

*EXCEPTIONS to re-trials may be considered by a Molina Medical Director and may require additional supporting documentation, discussion with the prescribing physician, or consultation with a physician affiliated with a transplant center, as deemed necessary by Molina Medical Director.

- Refer to **Appendix 2: Proposed Definitions for Statin-Related Muscle Disease**
For members not on ezetimibe (Zetia) therapy: [BOTH]

- Medical record documentation of a therapeutic failure on, intolerance to, or contraindication to ezetimibe (Zetia)
  - ACC/AHA guidelines recognize that maximal statin therapy may be inadequate to provide LDL-C reductions sufficient to reduce ASCVD risk in patients with primary severe elevations of LDL-C. In addition to a maximally tolerated dose of statin, non-statin cholesterol-lowering medications are recommended to lower LDL-C to acceptable levels in such cases (Stone 2014).
  - Ezetimibe (Zetia) is a non-statin included in a number of pivotal trials as a monotherapy comparator, add-on therapy to atorvastatin, and as a non-statin lipid modifying background therapy.

- If therapeutic failure on, intolerance to, or contraindication to ezetimibe (Zetia): Submit non-statin cholesterol-lowering medications regimen

- Adherence to Praluent (alirocumab) AND continued adherence maximally tolerated high-intensity statin therapy\(^B\) AND Zetia (ezetimibe) 10mg/day [as applicable to member therapy]
  Molina Reviewer: Verify member’s medication fill history for compliance on maximally tolerated high-intensity statin therapy AND Zetia (ezetimibe) 10mg/day

- Not prescribed for, or intended for, concurrent therapy with other PCSK9 Inhibitors [e.g. Repatha (evolocumab)]

Preferred PCSK9 Inhibitor: Repatha (evolocumab)
Clinically significant adverse event(s) or intolerance, FDA-labeled contraindication, or inadequate response after an adherent trial at an adequate therapeutic dose for at least three (3) months to the preferred PCSK9 inhibitor, Repatha (evolocumab). Documentation required: [ONE]

- Clinically significant adverse effect(s) or intolerance, including but not limited to:
  - Serious allergic reactions (e.g., rash, urticaria)\(^d\)
    - NOTE: For members with a documented latex allergy, Repatha Pushtronex once monthly may be utilized instead of Repatha (evolocumab) syringe or autoinjector
  - Intolerable adverse effects or drug toxicity impacting daily function/activities
    - Injection Site Reaction (includes erythema, pain, bruising) is not considered a clinically significant adverse reaction.
  - Persistent and uncorrectable problems with adherence to treatment as a result of significant intolerance
  - Poor clinical response to treatment documented by physical findings and/or clinical symptoms caused by adverse effects

- FDA-labeled contraindication
  - Serious hypersensitivity to evolocumab or any component of the formulation
    - Documentation of allergenic crossreactivity for PCSK9 inhibitors is limited. However, because of similarities in chemical structure and/or pharmacologic actions, the possibility of cross-sensitivity cannot be ruled out with certainty.\(^d\)

NOTE: The following conditions are not considered FDA-labeled contraindications of Repatha and does not meet above criterion: [ANY]
- Non-FDA approved use or dosage
- Pregnancy/Lactation
- Concurrent use of other PCSK9 inhibitors (e.g. evolocumab)
- Concurrent use with Juxtapid (lomitapide), Kynamro ( mipomersen)
Inadequate response* after an adherent trial (at least three (3) months) at the indicated therapeutic dose of Repatha (evolocumab) [*defined by: a percent change of less than 45% in LDL-C from baseline] supported by documentation of a recent LDL level within the past 30 days

This specific criterion is an additional Company requirement for coverage of the requested medication and will be denied if not met.

NOTE: If prescription claim(s) for the required step therapy drugs cannot be verified in the member’s prescription history, a copy of the physician chart note documenting the treatment failure or intolerance as defined above must be submitted for review.

NOTE: Current preferred biologics PCSK9 inhibitor Repatha (evolocumab). Molina Healthcare will only authorize one (1) biologic agent at a time.

5. Contraindications/Exclusions/Discontinuations to Praluent (alirocumab)
Authorization will not be granted if ANY of the following conditions apply [ANY]

☐ Non-FDA approved indications
☐ Hypersensitivity reactions (e.g., itching of the skin, rash, hives), including some serious events (e.g., hypersensitivity vasculitis, which is a skin rash that usually appears as purple-colored spots on the skin that is associated with inflammation of small blood vessels, and hypersensitivity reactions requiring hospitalization), have been reported with Praluent treatment

NOTE: For members with a documented latex allergy, Repatha Pushtronex once monthly may be utilized instead of Repatha (evolocumab) syringe or autoinjector

Exclusions

☐ Concurrent use of other PCSK9 inhibitors [e.g. Repatha (evolocumab)]
  ➢ Concurrent therapy with other PCSK9 inhibitors (e.g. evolocumab) has not been studied.

☐ Concurrent use with Juxtapid (lomitapide), Kynamro (mipomersen)
  ➢ Concurrent therapy with Juxtapid (lomitapide) or Kynamro (mipomersen) has not been studied.

6. Labs/Reports/Documentation required [ALL]
All documentation for determination of medical necessity must be submitted for review. Prescriber to submit medical records and specific labs, chart notes, and documentation as indicated in the criteria above. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

☐ Baseline LDL-C at the start of Praluent (alirocumab) therapy. Laboratory documentation required.
CONTINUATION OF THERAPY

Praluent (alirocumab) may be authorized for continuation of therapy if meet ALL of the following criteria are met: [ALL]

1. Initial Coverage Criteria

- Currently meets ALL initial coverage criteria
- Documented contraindication(s) to statin therapy [as documented in #5 in the ‘Initial Coverage Criteria’] OR continues to receive ONE (1) of the following: [ONE]
  - High-intensity statin [i.e. atorvastatin, Crestor (rosuvastatin)] at maximally tolerated dose
  - For members with documented intolerance to high-intensity statin: Low- or moderate-intensity statin (e.g. simvastatin, pravastatin) at maximally tolerated dose or alternative lower dose therapy of statins (i.e. reduction in dose, every other day dosing)

2. Compliance

- Adherence to Praluent (alirocumab) AND maximally tolerated high-intensity statin therapy AND Zetia (ezetimibe) 10mg/day as applicable to member therapy [as documented in #4 of the ‘Initial Coverage Criteria’]. Molina Reviewer: Verify member’s medication fill history for compliance and adherence (defined as filling ≥ 85% of the therapy at an FDA-approved dose in the recent authorization period)

  NOTE: Therapy may be discontinued due to poor adherence upon recommendation of the Molina Medical Director when adherence < 85% has been demonstrated in at least two months during the course of therapy

  NOTE: Statin adherence is required to avoid PCSK9 use as an alternative to statin non-adherence. Adherence to standard therapy is defined as filling ≥ 85% of therapy as prescribed in the recent authorization period.

- Tolerance (member should not experience severe adverse reaction(s) while on prescribed regimen)

3. Labs/Reports/Documentation required [ALL APPLICABLE]

Documentation of continued response to therapy as evidenced by:

- Recent LDL-C level (since the previous authorization and within the recent 3 months) demonstrating a clinically significant response to treatment [demonstrated a percent change of ≥ 45% in LDL-C from baseline (LDL-C before PCSK9 therapy)]
  - Measure LDL-C levels within 4 to 8 weeks of initiating or titrating Praluent to assess response and adjust the dose, if needed.
  - In Study 2 of pivotal trial, at week 12, the mean percent change from baseline in LDL-C was -45% with Praluent compared to 1% with placebo, and the treatment difference between Praluent (alirocumab) 75mg Q2W and placebo in mean LDL-C percent change was -46% (95% CI: -53%, -39%).
  - AHA/ACC guidelines note that with high-intensity statin therapy, LDL-C reductions ≥50% can be anticipated and used as an indicator of therapeutic response.
  - While clinical trials of alirocumab have shown decreases of LDL-C of 36-61% from baseline, it is difficult to assign a threshold value for the clinical significance of treatment specific to this drug. Indeed, recent guidelines for the treatment of blood lipids have moved away from the use of targeted levels of cholesterol reduction. Published literature describing non-responders to alirocumab was not found. [AMR Review 2015]
4. **Discontinuation of Treatment [ANY]**

Discontinue treatment if ANY of the following conditions applies: [ANY]

- Intolerable adverse effects or drug toxicity
- Persistent and uncorrectable problems with adherence to treatment
- Poor response to treatment as evidenced by physical findings and/or clinical symptoms
- Contraindications/Exclusions to therapy
  - Non-FDA approved indications
  - History of a serious hypersensitivity reaction to alirocumab
  - Hypersensitivity reactions (e.g., itching of the skin, rash, hives), including some serious events (e.g., hypersensitivity vasculitis, which is a skin rash that usually appears as purple-colored spots on the skin that is associated with inflammation of small blood vessels, and hypersensitivity reactions requiring hospitalization), have been reported with Praluent treatment.

**NOTE:** For members with a documented latex allergy, Repatha Pushtronex once monthly may be utilized instead of Repatha (evolocumab) syringe or autoinjector.

- Concurrent use of other PCSK9 inhibitors (e.g. evolocumab)
  - *Concurrent therapy with other PCSK9 inhibitors (e.g. evolocumab) has not been studied.*
- Concurrent use with Juxtapid (lomitapide), Kynamro (mipomersen)
  - *Concurrent therapy with Juxtapid (lomitapide) or Kynamro (mipomersen) has not been studied.*
1. Recommended Dosage [ALL]
   - The recommended starting dose is 75 mg administered subcutaneously once every 2 weeks, since the majority of patients achieve sufficient LDL-C reduction with this dosage: [ALL]
     - If the LDL-C response is inadequate, the dosage may be increased to the maximum dosage of 150 mg administered every 2 weeks.
     - Measure LDL-C levels within 4 to 8 weeks of initiating or titrating Praluent, to assess response and adjust the dose, if needed.

2. Authorization Limit [ALL]
   - Quantity limit: 2 syringes per 28 days. Maximum dosage of 150 mg every 2 weeks.
     - Initial authorization (3 months): 75 mg once every two weeks
     - For increase in dosage: Prescriber to submit LDL-C levels within 4 to 8 weeks of initiating or titrating Praluent for Medical/Pharmacy Director review
   - Dispensing limit: Only a 1-month supply may be dispensed at a time<sup>a-e</sup>
   - Duration of initial authorization: 3 months
   - Continuation of treatment: Re-authorization for continuation of treatment is required every 6 months to determine continued need based on documented positive clinical response
   - Duration of continuation of treatment: May be authorized up to six (6) months at a time.

3. Route of Administration [ALL]
   - Praluent (alirocumab) is considered a self-administered medication<sup>a</sup>
   - If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare. Self-administered medications may not be dispensed for self-administration and billed through the medical benefit by a provider; they must be dispensed through a participating pharmacy.

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**Coverage Exclusions**

Praluent (alirocumab) is considered experimental and investigational for indications that are not FDA-approved or included in ‘Coverage Criteria’ and is not a covered benefit addressed in this particular policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

- Pharmaceutical samples: The use of pharmaceutical samples (from the prescriber or manufacturer assistance program) will not be considered when evaluating the medical condition, prior prescription history, or as continuation of therapy.
Coronary heart disease (CHD) is a major cause of death in the United States. Elevated LDL-C is recognized as a major risk factor for cardiovascular disease. Approximately one-third of American adults have cardiovascular disease (CVD), making it the most common cause of death in the United States. Reduction of LDL-C has been shown to reduce cardiovascular morbidity and mortality. According to the Centers for Disease Control and Prevention, more than 71 million American adults (33.5%) have high LDL-C. A multinational survey of almost 10,000 patients with high cholesterol on statin therapy found approximately one-third of patients did not attain their LDL-C goal.

Familial hypercholesterolemia (FH) is an inherited condition that causes severe increases in total cholesterol and LDL-C. Individuals with FH are at a high risk for premature coronary artery disease. Homozygous FH is the more severe form of the disease affecting approximately 1 in 1,000,000 people while heterozygous FH affects approximately 1 in 500 people.

Heterozygous familial hypercholesterolemia (HeFH) is an inherited genetic disorder of lipid metabolism that affects about 1 in every 300 to 500 people. Based on that estimate there may be over 600,000 people with HeFH in the US. HeFH is characterized by lifelong elevated LDL-C levels due to defective LDL receptors that have reduced capacity for LDL-C uptake (Hopkins 2011). Compared with unaffected siblings, people with HeFH have approximately 2-fold higher LDL-C levels. Adult LDL-C levels are approximately 200 to 400 mg/dL (Reiner 2011). The goal of treatment for FH is to reduce the risk of coronary heart disease (CHD) or risk of a CHD equivalent condition (e.g. carotid artery disease, diabetes, peripheral arterial disease, or abdominal aortic aneurysm).

Hypercholesterolemia is a major public health issue in most countries as it contributes to the risk of developing cardiovascular disease and is the leading cause of death among men and women. Treatment of high cholesterol is aimed at lowering a patient’s LDL-C to reduce their risk of cardiovascular events, such as heart attacks and strokes.

HMG-CoA reductase inhibitors (statins) are a class of drugs that lower LDL through inhibition of HMG-CoA, an enzyme regulating the early and rate-limiting step in cholesterol biosynthesis that ultimately results in an increase in LDL receptors to increase the uptake of plasma LDL lipoproteins. Statins are a cornerstone of therapy for hyperlipidemia and have demonstrated effectiveness in considerable reduction of LDL-C levels. However, some patients do not respond adequately to statins, and others are unable to tolerate statin therapy due to side effects. Many patients continue to have cardiovascular events. It is estimated that five to 15 percent of patients are statin intolerant, primarily due to muscle-related side effects.

Statins include atorvastatin, pravastatin, simvastatin, fluvastatin, lovastatin, rosuvastatin, and pitavastatin. Existing non-statin therapies, as compared with statin therapy, do not provide acceptable ASCVD risk-reduction benefits relative to their potential for adverse effects in the routine prevention of ASCVD (2013 ACC/AHA). Existing non-statin therapies include niacin, bile acid sequestrants, fibrates, omega-3 fatty acids, and cholesterol absorption inhibitors. Therefore, novel non-statin, LDL-C-lowering therapies such as PCSK9 inhibitors are expected to meet this need.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) Inhibitor

PCSK9 is a circulating protein that binds to the LDL receptor and targets it for degradation. PCSK9 binds to the low-density lipoprotein receptors (LDLR) on the surface of hepatocytes to promote LDLR degradation within the liver. LDLR is the primary receptor that clears circulating LDL, therefore the decrease in LDLR levels by PCSK9 results in higher blood levels of LDL-C. By inhibiting the binding of PCSK9 to LDLR, alirocumab increases the number of LDLRs available to clear LDL, thereby lowering LDL-C levels.

Praluent (alirocumab) Alirocumab is a human monoclonal antibody (IgG1 isotype) that targets proprotein convertase subtilisin kexin type 9 (PCSK9). Alirocumab is a PCSK9 inhibitor produced by recombinant DNA technology in Chinese Hamster Ovary cell suspension culture. Alirocumab binds to PCSK9 enzyme which is present naturally in the body and decreases the metabolism of LDL by binding to the LDL receptor, mainly found in the liver.
Praluent (alirocumab) was approved by the U.S. Food and Drug Administration on July 24, 2015, as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of low density lipoprotein cholesterol (LDL-C). It is the first in the new class of PCSK9 (proprotein convertase subtilisin kexin type 9) inhibitors that lowers levels of LDL-C.

At the time of this writing, five of these trials have been published: Odyssey Mono, Odyssey Long Term, Odyssey Combo II, Odyssey Combo I, and Odyssey Options I.

**Efficacy**
The efficacy of Praluent (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 percent change in LDL-C from baseline).

**Safety**
The safety of Praluent (alirocumab) was evaluated in 9 placebo-controlled trials that included 2476 patients treated with Praluent, including 2135 exposed for 6 months and 1999 exposed for more than 1 year (median treatment duration of 65 weeks). At baseline, 37% of patients had a diagnosis of heterozygous familial hypercholesterolemia and 66% had clinical atherosclerotic cardiovascular disease. Adverse reactions led to discontinuation of treatment in 5.3% of patients treated with Praluent and 5.1% of patients treated with placebo. The most common adverse reactions leading to treatment discontinuation in patients treated with Praluent were allergic reactions (0.6% versus 0.2% for Praluent and placebo, respectively) and elevated liver enzymes (0.3% versus <0.1%).

**Hayes**
At the time of this writing, there was no Hayes Directory report or Hayes Rating available.

**Pivotal Trials**
Clinical trials have shown that PCSK9 inhibitors can lower LDL cholesterol significantly, and can be used either as monotherapy or in combination with other lipid-lowering drugs such as statins. When used as monotherapy, PCSK9 inhibitors can reduce LDL cholesterol by 50-60%, which is similar to the highest dosages of the most potent statins (such as atorvastatin and rosuvastatin). However, when used in combination with statins, PCSK9 inhibitors can reduce LDL cholesterol levels by an additional 50-70% compared to statins alone.

The Odyssey trials investigated multiple indications for alirocumab as both a monotherapy and a combination therapy with statins for lowering LDL-C in patients with primary hypercholesterolemia (HeFH or non-HeFH); in patients who are statin intolerant; and in patients with or without established coronary heart disease.

The efficacy of Praluent was investigated in five double-blind placebo-controlled trials that enrolled 3,499 patients; 36% were patients with HeFH and 54% were non-FH patients who had clinical atherosclerotic cardiovascular disease. All patients were receiving a maximally tolerated dose of a statin, with or without other lipid-modifying therapies. Study results showed that the treatment differences at week 24 between Praluent and placebo in mean LDL-C percent change were as follows:

- Study 1: -58% (P <0.0001)
- Study 2: -43% (P <0.0001)
- Studies 3 and 4 pooled: -54% (P <0.0001)
- Study 5: -36% (P <0.0001)
It should be noted that three studies used an initial dose of 75 mg every 2 weeks followed by criteria-based up-titration to 150 mg every 2 weeks 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 every 2 weeks dose.

**Phase III Odyssey Mono Trial (Roth and McKenney, 2015)**

Odyssey Mono was a randomized, double-blind, active comparator controlled trial comparing alirocumab monotherapy (n=52) with ezetimibe monotherapy (n=51) in patients with LDL-C level 100-190 mg/dL on no lipid-lowering therapy who had a moderate cardiovascular risk but no established coronary heart disease. The patient population was predominantly white (~90%); approximately half were male. Patients in the alirocumab treatment group received a starting dose of 75 mg self-administered subcutaneously every 2 weeks; the ezetimibe group took 10 mg orally once daily. Protocol dictated that patients in the alirocumab group be up-titrated to 150 mg at 8 weeks if their LDL-C was ≥ 100 mg/dL at week 8.

The primary efficacy endpoint was the percent difference between the 2 treatment groups in LDL-C from baseline to week 24, which was a statistically significant −31.6% favoring alirocumab over ezetimibe. LDL-C was reduced by 47.2% in the alirocumab group and by 15.6% in the ezetimibe group (P<0.0001). Of note, an administrative error resulted in 13 patients being incorrectly up-titrated to alirocumab 150 mg. These patients actually had LDL-C levels ≥ 70 mg/dL at 8 weeks. Only 1 of 14 patients up-titrated to 150 mg had an LDL-C ≥ 100 mg/dL at week 8. Investigators determined that this protocol violation did influence the primary endpoint outcome.

The most common adverse events in the alirocumab group were nasopharyngitis (23.1%), musculoskeletal and connective tissue disorders (15.4%), diarrhea (11.5%), and influenza (11.5%). These adverse events also occurred in the ezetimibe group: nasopharyngitis (15.7%), musculoskeletal and connective tissue disorders (21.6%), diarrhea (11.5%), and influenza (3.9%).


**Phase III Odyssey Combo II (Cannon et al., 2015).**

The COMBO II study compares the efficacy and safety of alirocumab versus the non-statin agent ezetimibe as add-on therapy to maximally tolerated statin therapy in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia. The COMBO II is a double-blind, double-dummy, active-controlled, parallel-group, 104-week study that is conducted at 126 sites. Patients (n=720) were randomized to either 75 mg subcutaneous alirocumab every 2 weeks (plus oral placebo) or 10 mg daily oral ezetimibe (plus subcutaneous placebo).

**Main results**

- After 24 weeks, a reduction in LDL-C of 50.6% was seen with alirocumab, and 20.7% with ezetimibe, both in addition to maximum tolerated statin treatment (LS mean difference (SE) vs. ezetimibe: -29.8% (2.3) P <0.0001).
- 77.0% of the patients achieved LDL-C target levels <1.8 mmol/L, compared to 45.6% of the ezetimibe-treated patients (P< 0.0001).
- 18% of patients randomized to alirocumab needed dose adjustment based on their LDL-C levels at week 12.
- The LDL-C decrease achieved with alirocumab was stable during the 52-week follow-up.
- These results were consistent across various patient subgroups.
- Typical statin-related adverse events were equally seen in the treatment arms. Small numerical differences in relevant side effects were observed, like more verified CV events (4.8% vs. 3.7% in alirocumab vs. ezetimibe), more injection-site reactions (2.5% vs. 0.8% with placebo injection), less neurocognitive disorders (0.8 % vs. 1.2%), more often ALT> 3x ULN (1.7% vs. 0.4%) and creatine kinase> 3x ULN (2.8% vs. 2.5%). The alirocumab injections were generally well tolerated and compliance with self-injections was good.

Results: Adding alirocumab to a treatment regimen with maximally tolerated statins provided safe and substantial LDL-C reductions and more patients with hypercholesterolemia can achieve LDL-C goals than by adding ezetimibe. These results are in line with the previous suggestion that maximum LDL-C response to a PCSK9 inhibitor is greater with combination therapy than with monotherapy. The COMBO II study is ongoing and will continue up to 104 weeks follow-up to maximize the available safety data and generate information on the durability of alirocumab lipid-lowering effects.
Odyssey Options I (Bays et al., 2015)
Results from Odyssey Options I (n=355) published in Journal of Clinical Endocrinology and Metabolism. Adding alirocumab to atorvastatin provided greater LDL-C reductions vs. adding ezetimibe, doubling atorvastatin dose, or switching to rosuvastatin (p<0.001 vs. all comparators), and enabled greater LDL-C goal achievement.

Treatment-emergent adverse events occurred in 65.4% of alirocumab patients, vs 64.4% ezetimibe and 63.8% double atorvastatin/switch to rosuvastatin (data pooled).

Odyssey Long Term Trial (Robinson et al., 2015)
Odyssey Long Term was a randomized, double-blind, placebo-controlled study comparing alirocumab 150 mg subcutaneously every 2 weeks (n=1553) with placebo (n=788) in patients with LDL-C ≥ 70 mg/dL on high-dose statin therapy, or statin therapy at the maximum tolerated dose, with or without other lipid-lowering therapy. Injections were performed by the patient or designated caregiver. The study population was predominantly white (93%) and the majority were male (62%). A total of 47% of patients were on a high-dose statin, and 28% were on other lipid-lowering therapy; 14% were on ezetimibe.

Summary of Odyssey Long Term Trial
Addition of alirocumab to statin therapy may reduce low-density lipoprotein cholesterol levels in patients at high risk of cardiovascular events

- 2,341 adults (mean age 60 years) at high risk of cardiovascular events who had low-density lipoprotein (LDL) cholesterol levels ≥ 70 mg/dL (≥ 1.8 mmol/L) while on statin therapy were randomized 2:1 to alirocumab 150 mg vs. placebo subcutaneously every 2 weeks for 78 weeks
- Patients had heterozygous familial hypercholesterolemia, established coronary heart disease (CHD), or CHD risk factors and continued statin therapy with or without other lipid-lowering therapy during trial
- All patients were instructed to follow Therapeutic Lifestyle Changes diet or equivalent diet for duration of trial
- Mean baseline LDL cholesterol levels 122 mg/dL (3.2 mmol/L)
- 27% discontinued trial (25% due to adverse events, 16% due to nonadherence, and 59% due to other reasons)
- 98.7% had cholesterol data available through week 24 and were included in efficacy analyses
- Comparing alirocumab vs. placebo
  - LDL cholesterol < 70 mg/dL at 24 weeks in 79.3% vs. 8% (p < 0.001, NNT 2)
  - nonfatal myocardial infarction in 0.9% vs. 2.3% (p = 0.01, NNT 72)
  - serious adverse event in 18.7% vs. 19.5% (not significant)
  - adverse events leading to discontinuation in 7.2% vs. 5.8% (not significant)
- Alirocumab associated with significantly improved lipid profile at 24 weeks
- No significant differences in other confirmed cardiovascular adverse events

Primary efficacy endpoint: The percentage change in LDL-C from baseline to week 24; the alirocumab group demonstrated a 61% mean reduction in LDL-C, compared with a 0.8% mean increase in high-density lipoprotein (HDL-C) in the placebo group (P<0.001).

Most common adverse events associated with alirocumab included allergic reaction (10.1%), local injection site reaction (5.9%), myalgia (5.4%), and neurologic events (4.2%). A total of 65 patients experienced neurologic adverse events; of these, only 5 were serious adverse events, including ataxia (n=1), demyelination (n=1), dysarthria (n=1), Miller Fisher syndrome (n=1), and optic neuritis (n=1).

**Odyssey Combo I (Kereiakes et al., 2015)**

The Odyssey Combo I study (http://clinicaltrials.gov/show/NCT01644175) evaluated efficacy and safety of alirocumab as add-on therapy to stable maximally tolerated daily statin with or without other lipid-lowering therapy in high cardiovascular risk patients with sub-optimally controlled hypercholesterolemia.

This multicenter, phase 3, randomized (2:1 alirocumab vs placebo), double-blind, 52-week trial enrolled 316 patients with established coronary heart disease or coronary heart disease risk equivalents and hypercholesterolemia. Alirocumab (75 mg every 2 weeks [Q2W]) or placebo Q2W was self-administered subcutaneously via 1 mL prefilled pen. The alirocumab dose was increased to 150 mg Q2W (also 1 mL) at week 12 if week 8 low-density lipoprotein cholesterol (LDL-C) was ≥70 mg/dL. The primary efficacy end point was percent change in LDL-C from baseline to week 24 (intent-ion-to-treat analysis).

Results: At week 24, estimated mean (95% CI) changes in LDL-C from baseline were −48.2% (−52.0% to −44.4%) and −2.3% (−7.6% to 3.1%) for alirocumab and placebo, respectively, an estimated mean (95% CI) difference of −45.9% (−52.5% to −39.3%) (P < .0001). Low-density lipoprotein cholesterol <70 mg/dL was achieved by 75% alirocumab versus 9% placebo patients at week 24. At week 12, 83.2% of evaluable alirocumab-treated patients remained on 75-mg Q2W. Treatment-emergent adverse events were comparable between groups.

Conclusions: Alirocumab treatment achieved a significantly greater reduction in LDL-C and allowed a greater proportion of patients to achieve LDL-C goals, versus placebo after 24 weeks in high cardiovascular risk patients with sub-optimally controlled hypercholesterolemia at baseline despite receiving maximally tolerated statin with or without other lipid-lowering therapy. The frequency of treatment-emergent adverse events and study medication discontinuations were generally comparable between treatment groups.

*Available at: [http://www.ahjonline.com/article/S0002-8703(15)00168-4/fulltext]*

**ODYSSEY ALTERNATIVE**

Study of Alirocumab in Patients With Primary Hypercholesterolemia and Moderate, High, or Very High Cardiovascular (CV) Risk, Who Are Intolerant to Statins

Odyssey Alternative is the first trial of a PCSK9 inhibitor to reassess statin intolerance, as measured by skeletal muscle AEs, by including a validation arm (atorvastatin 20 mg). The study randomized 314 patients to either alirocumab (75 mg self-administered injection every two weeks), ezetimibe (10 mg/day) or atorvastatin (20 mg/day) arms for 24 weeks. The alirocumab dose was increased to 150 mg at week 12 depending on cardiovascular risk and week 8 LDL-C levels.

In clinical practice, 10 to 25 percent of patients report intolerance to statins, and many have poorly-controlled LDL-C, which puts them at greater risk of CV events. In this trial, there were fewer skeletal muscle AEs in the alirocumab group compared to patients treated with atorvastatin (32.5 percent versus 46 percent, hazard ratio = 0.61; nominal p value = 0.042), and there was no significant difference when compared to the ezetimibe group (41 percent). In addition, there were numerically fewer discontinuations for skeletal muscle AEs in the alirocumab group, but this did not reach statistical significance (alirocumab 16 percent, ezetimibe 20 percent, atorvastatin 22 percent). In comparison, the overall rate of discontinuations for skeletal muscle AEs across the Phase 2 and 3 alirocumab placebo-controlled studies, where the majority of patients were also on statins, was 0.4 percent for alirocumab (n=2,476) and 0.5 percent for placebo (n=1,276).

**ODYSSEY ALTERNATIVE** evaluates efficacy and safety of alirocumab, a fully human proprotein convertase subtilisin/kexin type 9 monoclonal antibody, in patients with well-documented statin intolerance and moderate to very high cardiovascular risk.

- Includes patients unable to tolerate at least 2 statins, 1 at lowest starting dose
- Intolerance reaffirmed via placebo run-in and blinded statin re-challenge
- The only PCSK9 inhibitor study in a well-defined statin-intolerant population
- Alirocumab compared with ezetimibe
Statin intolerance is defined in this study as the inability to tolerate at least 2 different statins because of unexplained skeletal muscle-related symptoms, such as pain, aches, weakness, or cramping that began or increased during statin therapy and returned to baseline when statin therapy was discontinued. For each patient to meet this definition, one of the statins that was discontinued had to have been at the lowest approved daily starting dose (i.e., rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, pitavastatin 2 mg); the other statin was at any dose.

Diagnosis of heterozygous familial hypercholesterolemia in this study was made by genotyping or, if genotyping was not available, by clinical criteria (investigators could choose to use the Simon Broome3 or the World Health Organization/Dutch Lipid Network20 criteria).

Hyperlipidemia Treatment Guideline (Reference ‘Appendix’ for Summary of Additional Guidelines)

The American College of Cardiology/American Heart Association (ACC/AHA)

https://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a.full.pdf

Recent guidelines released in November 2013, the American College of Cardiology/American Heart Association (ACC/AHA) updated Policy for the treatment of blood cholesterol and recommended intensive statin treatment (defined as atorvastatin 40-80 mg or rosuvastatin 20-40 mg daily) in patients with established coronary heart disease. The new guidelines:

- Remove treatment targets for LDL-C for primary or secondary prevention of atherosclerotic cardiovascular disease (ASCVD)
- Recommend high- or moderate-intensity statin therapy based on patient risk factors

The stated rationale for removing LDL-C treatment targets is that no studies have focused on treatment or titration to a specific LDL-C goal in adults with clinical ASCVD. The majority of randomized controlled studies confirming the efficacy of cholesterol reduction in improving clinical outcomes in patients with clinical ASCVD used a single fixed-dose statin therapy to lower LDL-C levels.

DEFINITIONS

1. ASCVD, or atherosclerotic cardiovascular disease, is caused by plaque buildup in arterial walls and refers to the following conditions:
   - Coronary heart disease (CHD), such as myocardial infarction (MI), angina, and coronary artery stenosis greater than 50%.
   - Cerebrovascular disease, such as transient ischemic attack (TIA), ischemic stroke, and carotid artery stenosis greater than 50%.
   - Peripheral artery disease, such as claudication.
   - Aortic atherosclerotic disease, such as abdominal aortic aneurysm (AAA) and descending thoracic aneurysm.

   ➢ Primary prevention refers to the effort to prevent or delay the onset of ASCVD disease.
   ➢ Secondary prevention refers to the effort to treat known, clinically significant ASCVD disease, and to prevent or delay the onset of disease manifestations.

2. Dyslipidemia is a broad term describing a number of conditions, including hypercholesterolemia, hyperlipidemia and mixed dyslipidemia, in which disturbances in fat metabolism lead to changes in the concentrations of lipids in the blood. Along with other risk factors, dyslipidemia may lead to the development of atherosclerosis and cardiovascular disease.

3. Familial hypercholesterolemia (FH) is an inherited condition caused by genetic mutations which lead to high levels of LDL-C at an early age. Patients can have either one of two types of FH. Heterozygous FH is the more common type of FH and can cause LDL-C levels twice as high as normal (e.g., >190 mg/dL). Individuals with HeFH have one altered copy of a cholesterol-regulating gene. Homozygous FH is the rare, more severe form, occurring in approximately one in a million individuals. It has been reported that HoFH can cause LDL-C levels more than six
times as high as normal (e.g., 500-1,000 mg/dL). An individual with HoFH has two altered copies of cholesterol-regulating genes (one from each parent).

4. **Hypercholesterolemia** is defined as a raised level of cholesterol in the blood, typically including elevated low-density lipoprotein cholesterol (LDL-C).

5. **Hyperlipidemia** refers to raised cholesterol and/or raised triglycerides, and mixed dyslipidemia is a wider term that encompasses hyperlipidemia as well as decreased levels of high-density lipoprotein cholesterol (HDL-C).

6. **Lipidologist** is a certified physician specializing in the prevention of dyslipidemia (cholesterol and other lipid disorders) or related metabolic diseases (such as diabetes) which often lead to heart disease, stroke or atherosclerosis (vascular disease). Physicians who have passed a rigorous credentialing and examination process can be certified in clinical lipidology. Such members carry the designation Diplomate, American Board of Clinical Lipidology and are considered by the NLA to be lipidologists. (Please visit www.lipidboard.org for more information.)

7. **Simon Broome Register criteria:** A list of criteria used to diagnose familial hypercholesterolemia. Definitive diagnosis according to Simon Broome diagnostic criteria include total cholesterol concentrations >6.7 mmol/l or LDLc > 4.0 mmol/l in children or total cholesterol > 7.5 mmol/l or LDLc > 4.9 mmol/l in adults and tendon xanthoma; evidence of these signs in first or second degree relative; or DNA evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation.


### APPENDIX

#### Appendix 1: STATIN INTENSITY CHART

Recommendations are from the American Heart Association (AHA) 2013 guidelines on the treatment of blood cholesterol. All guidelines pertain to adult patients only.

<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>lowers cholesterol by ≥50%</td>
<td>lowers cholesterol by 30 - 50%</td>
<td>lowers cholesterol by &lt; 30%</td>
</tr>
<tr>
<td>Atorvastatin (Lipitor®): 40 - 80mg per day</td>
<td>Atorvastatin (Lipitor®) 10 - 20mg per day</td>
<td>Simvastatin (Zocor®) 10mg per day</td>
</tr>
<tr>
<td>Rosuvastatin (Crestor®) 20 - 40mg per day</td>
<td>Rosuvastatin (Crestor®) 5 - 10mg per day</td>
<td>Pravastatin (Pravachol®) 10 - 20mg per day</td>
</tr>
<tr>
<td>Simvastatin (Zocor®) 20 - 40mg per day</td>
<td>Simvastatin (Zocor®) 5 - 10mg per day</td>
<td>Lovastatin (Mevacor®) 20mg per day</td>
</tr>
<tr>
<td>Pravastatin (Pravachol®) 40 - 80mg per day</td>
<td>Pravastatin (Pravachol®) 20 - 40mg per day</td>
<td>Fluvastatin (Lescol®) 20 - 40mg per day</td>
</tr>
<tr>
<td>Lovastatin (Mevacor®) 40mg per day</td>
<td>Lovastatin (Mevacor®) 20mg per day</td>
<td>Fluvasatin (Lescol®) 40mg twice per day</td>
</tr>
<tr>
<td>Fluvastatin XL (Lescol XL®) 80mg per day</td>
<td>Fluvastatin XL (Lescol XL®) 80mg per day</td>
<td>Pitavastatin (Livalo®) 1mg per day</td>
</tr>
<tr>
<td>Fluvastatin (Lescol®) 40mg twice per day</td>
<td>Pitavastatin (Livalo®) 2 - 4mg per day</td>
<td></td>
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</tbody>
</table>

*Simvastatin 80 mg dose is available, but is associated with increased risk of muscle injury and should not be started in new patients. Only patients taking simvastatin 80 mg for ≥ 12 months without evidence of muscle injury should continue this dose*

Reference: For the full ACC/AHA guideline for the treatment of blood cholesterol to reduce ASCVD risk in adults, refer to: http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a
Neither the ACC/AHA/NHLBI nor the NLA recommends routine CK level monitoring in all patients after beginning statin therapy, but instead recommends obtaining CK level only in patients who develop muscle symptoms while on statin therapy.¹,² The NLA does not recommend baseline monitoring of CK levels for all patients, as they report that this is not cost-effective. The NLA does recommend obtaining baseline CK levels only in patients at high risk for myopathy, such as older patients or those requiring combination therapy with another agent known to increase myotoxicity.²

The ACC/AHA/NHLBI recommends discontinuation of statin therapy if the CK level obtained in a symptomatic patient is >10 × ULN.

If the CK level obtained in a symptomatic patient is <10 × ULN but muscle symptoms are tolerable, statin therapy can be continued with or without a dose reduction and symptoms can be used as a clinical guide to stop or continue statin therapy from that point forward.

If a patient develops rhabdomyolysis, defined as a CK level >10 × ULN or >10,000 IU/L with an elevation in serum creatinine or a requirement for IV hydration therapy, statin therapy should be discontinued immediately.²

References:
Appendix 3: Guideline Recommendations for Cholesterol Management with LDL Levels

- **American Association of Clinical Endocrinologists (AACE).** The 2012 update of the AACE Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis were developed according to the AACE Protocol for Standardized Production of Clinical Practice Guidelines–2010 update.
  - AACE recommends a target LDL-C concentration less than 100 mg/dL and less than 70 mg/dL in all patients at very high risk.
  - AACE recommends aggressive lipid-modifying therapy to lower LDL-C to less than 100 mg/dL in patients with average or elevated LDL-C. This has been shown to reduce vascular mortality in patients at high risk and to decrease coronary death, MI, or any cardiovascular events in patients on aggressive statin therapy
  - AACE recommends an LDL-C goal less than 70 mg/dL as an appropriate goal for all patients with established CAD.
  - AACE recommends statins as the drug of choice for LDL-C reduction on the basis of findings from morbidity and mortality outcome trials.


- **The American Diabetes Association (ADA)** standards of care for diabetes state that statin therapy should be initiated in individuals with diabetes and other cardiovascular risk factors with a target LDL cholesterol of <100 mg/dl. Furthermore, a possible target LDL of <70 mg/dl is stated in patients with diabetes and cardiovascular disease.

- **The 2004 update of the Adult Treatment Panel (ATP) III of the National Cholesterol Education Program (NCEP)** recommended an LDL-C goal <100 mg/dL for high-risk patients, with an optional goal of <70 mg/dL for very high-risk patients. This update also recommended initiating dietary therapy and LDL-C-lowering drugs for all patients over goal, with a planned LDL-C reduction of 30% to 40%. The rationale for these changes was based on several randomized clinical trials, the results of which were published after the release of the ATP III guidelines (Grundy 2004).

- **The National Lipid Association** set a primary prevention goal of non-HDL cholesterol <130 mg/dL and LDL cholesterol <100 mg/dL. The secondary prevention goal is non-HDL cholesterol <100 mg/dL and LDL cholesterol <70 mg/dL if the patient has ASCVD or diabetes and in addition to ≥2 major ASCVD risk factors.


  The International Atherosclerosis Society (IAS) Position Paper on Global Recommendations for the Management of Dyslipidemia was published online in July 2013, and recommendations were based on international consensus among experts from multiple regions around the world.

  The IAS defines "optimal levels" of atherogenic lipoproteins in primary and secondary prevention, which are identical to those of ATP III, but does not provide specific treatment goals.

  According to the IAS, “high risk can be defined as one of the following: (a) a risk for ASCVD > 45% up to age 80, (b) diabetes plus other risk factors (Solano and Goldberg 2006), (c) familial hypercholesterolemia (Civeira 2004), and possibly chronic kidney disease (Polonsky and Bakris 2012). For primary prevention, current guidelines generally agree cholesterol levels in high-risk persons should be lowered to the optimal range (Grundy et al. 2004; Catapano et al 2011; Anderson et al. 2013).”
Recommendation: Optimal levels for LDL-C and non-HDL-C in secondary prevention are < 70 mg/dL (1.8 mmol/L) and < 100 mg/dL (2.6 mmol/L), respectively.

**European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS)**

In July, 2014, the EAS published a consensus statement for the screening and treatment of homozygous FH. The treatment recommendations are summarized as follows:

- Treatment of homozygous FH involves a combination of lifestyle changes, statin therapy, and lipoprotein apheresis, if available, and should be started as early as possible.
- LDL apheresis should begin as early as age 5 years and no later than age 8 years.
- For homozygous FH patients, the LDL cholesterol targets are < 100 mg/dL for adults, < 70 mg/dL for adults with clinical CVD, and < 135 mg/dL for children.
- Two novel agents for LDL cholesterol lowering, lomitapide and mipomersen, can be considered as adjunctive treatments for patients who do not achieve the recommended LDL cholesterol targets and remain at high cardiovascular risk.

*Reference: European Atherosclerosis Society. New EAS Consensus Panel Statement on Homozygous FH.*

Similar to NCEP ATP III and IAS, the ESC/EAS guidelines recommend that the intensity of lipid therapy be adjusted to the level of risk.

- LDL-C is recommended as the primary target of therapy. In agreement with the NCEP ATP III update, for patients at very high risk (established ASCVD, diabetes, chronic kidney disease (CKD), or 10-year total ASCVD risk of ≥10% by SCORE), the target LDL-C level is <70 mg/dl or ≥50% reduction when target level cannot be reached.
- For patients at high ASCVD risk (markedly elevated single ASCVD risk factor or SCORE ≥5 to <10%) an LDL-C goal of <100 mg/dl is suggested. In patients with the metabolic syndrome, diabetes, or CKD with combined dyslipidemias, the ESC/EAS guidelines suggest that non–HDL-C or Apo B may be measured and considered as a secondary target of therapy, similar to recommendations of the NCEP ATP III update for assessment of non–HDL-C.

**The National Institute for Health and Care Excellence (NICE) Guidelines**

In July 2014, NICE published its Policy (CG181) on cardiovascular risk and lipid modification. In particular, the advice given for starting statin therapy is that this should only be done after an informed discussion between the clinician and the patient about the risks and benefits of treatment. The 2014 NICE guidelines (CG181) also take into account additional factors in deciding to start statin therapy, such as potential benefits from lifestyle modifications, informed patient preference, co-morbidities, other medications and life expectancy. NICE recommended statin therapy based on other clinical risk factors for CAD, rather than by LDL-C measurement alone.


**Appendix 4: ACC/AHA Guidelines Differences for Cholesterol Management**

In 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) released joint cholesterol management guidelines. A year later, the National Lipid Association (NLA) released their own set of cholesterol guidelines that differed from the ACC/AHA recommendations. Although both guidelines are patient-centric and intended for adults ≥18 years of age, there are significant differences.

The 2004 update of the Adult Treatment Panel (ATP) III of the National Cholesterol Education Program (NCEP) established a target goal of < 100 mg/dL for high-risk patients and an optional target of <70 mg/dL for very high-risk patients (Grundy 2004). Recent guidelines released by the American College of Cardiology (ACC) and American Heart Association (AHA) have moved away from absolute target goals, opting instead to recommend relative LDL-C reductions of 30% to ≥ 50% for high-risk patients.

The ACC/AHA Task Force on Practice Guidelines reported that in the absence of randomized clinical trials titrating drug therapy to specific LDL-C levels, there is no clear indication of what the target should be. The panel was also concerned about the potential adverse effects that might occur in an attempt to achieve specific goals (Stone 2014). The National
Lipid Association (NLA) and American Diabetes Association (ADA), however, still adhere to target levels for high-risk and very high-risk patients (ADA 2014, Jacobson 2014).

- **The ACC/AHA guidelines (Stone 2014)**
  One of the major controversies is that the ACC/AHA guidelines do not make recommendations for specific LDL cholesterol goals or non–high-density lipoprotein (HDL) cholesterol goals for primary and secondary ASCVD prevention. Monitoring of LDL-C with follow-up laboratory data is recommended in the 2013 ACC/AHA guidelines; however the value is to be used only as an assessment of compliance and response to treatment rather than as a target of therapy.

- **National Lipid Association (NLA) Recommendations** include 4 leading principles: (1) patients with dyslipidemia require lifestyle intervention in an effort to reduce the risk of ASCVD, regardless of pharmacotherapy; (2) intensity of risk reduction therapy should be adjusted to a patient’s absolute risk for an ASCVD event; (3) statin therapy is the primary modality for reducing ASCVD risk unless contradicted; and (4) other ASCVD risk factors should be managed appropriately.

  The NLA guidelines set a primary prevention goal of non-HDL cholesterol <130 mg/dL and LDL cholesterol <100 mg/dL. The secondary prevention goal is non-HDL cholesterol <100 mg/dL and LDL cholesterol <70 mg/dL if the patient has ASCVD or diabetes and in addition to ≥2 major ASCVD risk factors.


### Appendix 5: Non-Statins, ezetimibe plus a statin

- In two randomized, double-blind, placebo-controlled trials, ezetimibe at a dose of 10 mg/day reduced LDL-C by approximately 17 percent [1,2]. Ezetimibe is also effective as adjunctive therapy to a statin [3-7]; in one study, a 10 mg dose of ezetimibe lowered LDL-C by 14 percent above the LDL lowering effect of simvastatin [5].

- IMPROVE-IT, the first large trial to directly assess clinical outcomes with ezetimibe plus a statin compared with a statin alone, found that after a median follow-up of six years, patients with an acute coronary syndrome randomized to ezetimibe/simvastatin had a lower rate of the primary composite CV outcome (CV death; MI; hospital admission for unstable angina; coronary revascularization 30 or more days after randomization; or stroke) than those randomized to simvastatin alone (hazard ratio [HR] 0.94, 95% CI 0.89-0.99; seven-year event rates 32.7 versus 34.7 percent) [42]. All-cause mortality (HR 0.99) and CV mortality (HR 1.00) were not reduced. Adverse events were similar in the two arms. The benefits on CV endpoints provide support for LDL-C lowering with this inhibitor of NPC1L1. [Cannon CP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med 2015; 372:2387.]

Summary of IMPROVE-IT: First trial demonstrating incremental clinical benefit when adding a non-statin agent (ezetimibe) to statin therapy:

- Non-statin lowering LDL-C with ezetimibe reduces cardiovascular events
- Even Lower is Even Better (achieved mean LDL-C 53 vs. 70 mg/dL at 1 year)
- Confirms ezetimibe safety profile
- Reaffirms the LDL hypothesis, that reducing LDL-C prevents cardiovascular events

Reference: Rosenson, Robert S. Statin myopathy. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2013. Accessed March 2015. Primary references cited by article:


NICE clinical guideline 71 [Policy.nice.org.uk cg71]
Recommendations from 'Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia' (NICE technology appraisal Policy 132) and incorporated into this guideline in line with NICE procedures for developing clinical guidelines.

- Ezetimibe monotherapy is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolemia who would otherwise be initiated on statin therapy but who are unable to do so because of contraindications to initial statin therapy[2].
- Ezetimibe, coadministered with initial statin therapy, is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolemia who have been initiated on statin therapy when[3]:
  - serum total or LDL-C concentration is not appropriately controlled (as defined in recommendation 1.3.1.10) either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy (as defined in recommendation 1.3.1.11) and
  - consideration is being given to changing from initial statin therapy to an alternative statin.

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Clinical Trials, Definitions, Peer-Reviewed Publications


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- Roth EM, McKenney JM. ODYSSEY MONO: effect of alirocumab 75 mg subcutaneously every 2 weeks as monotherapy versus ezetimibe over 24 weeks. Future Cardiol. 2015;11(1):27-37.

**Government Agencies, Professional Societies, and Other Authoritative Publications**


U.S. Guidelines

- American College of Cardiology/American Heart Association (ACC/AHA) guidelines on treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults can be found in Circulation 2014 Jun 24;129(25 Suppl 2):S1, also published in J Am Coll Cardiol 2014 Jul 1;63(25 Pt B):2889 PDF, synopsis of major recommendations can be found in Ann Intern Med 2014 Mar 4;160(5):339
  - assessment of cardiovascular risk can be found in J Am Coll Cardiol 2014 Jul 1;63(25 Pt B):2935 PDF
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- American Heart Association (AHA) scientific statements on triglycerides and cardiovascular disease can be found in Circulation 2011 May 24;123(20):2292
  - managing abnormal blood lipids can be found in Circulation 2005 Nov 15;112(20):3184
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- Institute for Clinical Systems Improvement (ICSI) guideline on lipid management in adults can be found at ICSI 2013 Nov PDF or at National Guideline Clearinghouse 2014 May 26:47783
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Guidelines in Children and Adolescents

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- Health Care for the Homeless Clinician's Network guideline on treatment and recommendations for homeless patients with hypertension, hyperlipidemia, and heart failure can be found at HCHCN 2009 PDF
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