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Medication Policy Manual

Policy No: dru697

Topic: PCSK9 Inhibitors

- Leqvio, inclisiran
- Praluent, alirocumab
- Repatha, evolocumab

Date of Origin: June 1, 2022

Committee Approval Date: March 16, 2023

Next Review Date: 2024

Effective Date: June 1, 2023

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

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are used in the treatment of atherosclerotic cardiovascular disease (ASCVD) and familial hypercholesteremia.

Policy/Criteria

Most contracts require pre-authorization approval of PCSK9 inhibitors prior to coverage.

I. Continuation of therapy (COT): PCSK9 inhibitors may be considered medically necessary for COT when criteria A, B, or C **AND** D below is met.

A. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

D. **For Leqvio (inclisiran) only:** Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): PCSK9 inhibitors may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A and B below are met.

A. **Leqvio (inclisiran) only:** Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

AND

B. At least one of the following diagnostic criterion 1, 2 or 3 below is met.

1. **Leqvio (inclisiran), Praluent (alirocumab), Repatha (evolocumab): Heterozygous familial hypercholesterolemia** (HeFH) when both criteria a and b are met.

a. The requested PCSK9 inhibitor has been prescribed by or in conjunction with a specialist in cardiology or lipid management and there is clinical documentation of at least one of the following (i, ii, or iii):

i. A definitive diagnosis of FH using Simon Broome diagnostic criteria or Dutch Lipid Clinic Network criteria (see *Appendices 1 and 2*).

OR

ii. An untreated low-density lipoprotein cholesterol (LDL-C) 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

iii. Presence of a causal mutation for FH by DNA testing (e.g., a mutation in the *LDLR, APOB, PCSK9,* or *LDLRAP1* genes).

AND

b. 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. The treatment regimen must include all the following (i, ii, and iii), unless contraindicated or not tolerated:

i. A high-intensity statin (atorvastatin or rosuvastatin). If one high-intensity statin has not been tolerated due to statin-associated side effects, then at least one other statin must have been tried at a lower dose.

AND

ii. Ezetimibe.

AND

iii. **For Leqvio (inclisiran) only:** Praluent (alirocumab) or Repatha (evolocumab).

OR

2. **Praluent (alirocumab) or Repatha (evolocumab) only: homozygous familial hypercholesterolemia** (HoFH) when criteria a and b below are met:

a. The requested PCSK9 inhibitor has been prescribed by or in conjunction with a specialist in cardiology or lipid management and there is clinical documentation of at least one of the following (i or ii):

i. Genetic confirmation of two mutant alleles at the *LDLR, APOB, PCSK9,* or *LDLRAP1* gene locus.

OR

ii. An untreated low-density lipoprotein cholesterol (LDL-C) of > 500 mg/dL (or a treated LDL-C of > 300 mg/dL) with either (1 or 2):

1. Cutaneous or tendon xanthoma before age 10 years.

OR

2. Evidence of heterozygous familial hypercholesterolemia in both parents.

AND

b. Treatment with maximally tolerated statin therapy has been ineffective, contraindicated, or not tolerated.

OR

3. Leqvio (inclisiran), Praluent (alirocumab), Repatha (evolocumab): clinical atherosclerotic cardiovascular disease (ASCVD) when criteria a, b, and c below are met (see *Appendix 6* for definitions of ASCVD).

a. The requested PCSK9 inhibitor has been prescribed by or in conjunction with a specialist in cardiology or lipid management.

AND

b. The member is at very high risk for ASCVD events (see *Appendix 8*).

AND

c. Treatment with maximally tolerated lipid lowering therapy has failed to achieve an LDL-C of less than or equal to 70 mg/dL after at least 12 weeks of therapy. The treatment regimen must include <u>all the following</u> (i, ii, and iii), unless contraindicated or not tolerated.

i. A high-intensity statin (atorvastatin or rosuvastatin). If one high-intensity statin has not been tolerated due to statin-associated side effects, then at least one other statin must have been tried at a lower dose.

AND

ii. Ezetimibe.

AND

iii. **For Leqvio (inclisiran) only:** Praluent (alirocumab) or Repatha (evolocumab).

III. Administration, Quantity Limitations, Authorization Period

A. Regence Pharmacy Services considers Praluent (alirocumab) and Repatha (evolocumab) to be coverable only under the pharmacy benefit (as self-administered medications).

B. Regence Pharmacy Services considers Leqvio (inclisiran) to be coverable only

under the medical benefit (as a provider-administered medication).

C. When pre-authorization is approved, PCSK9 inhibitors will be authorized in the following quantities:

Medication	Authorization Limit
Praluent (alirocumab)	Up to 150 mg every 2 weeks or 300 mg every 4 weeks.
Repatha (evolocumab)	Up to 140 mg every other week or 420 mg once monthly.
Leqvio (inclisiran)	Loading Dose: Up to 284 mg initially followed by 284 mg in 3 months. Maintenance Dose: Up to 284 mg every 6 months.

D. Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. PCSK9 inhibitors are 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.

V. PCSK9 inhibitors are considered investigational when used for all other conditions, including but not limited to:

A. In combination with other PCSK9 inhibitors or Juxtapid (lomitapide).

Position Statement

Summary

- Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are subcutaneous medications indicated:
  - to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease.
  - as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia, HeFH) to reduce low-density lipoprotein cholesterol (LDL-C).
  - 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.
- The intent of this policy is to limit coverage of PCSK9 inhibitors to patients with a confirmed diagnosis of HoFH, HeFH, or clinical ASCVD, who have tried and failed lower cost therapies (as detailed in the coverage criteria).
- 2018 AHA/ACC Guidelines on the Management of blood cholesterol 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%. Statins have been proven to reduce cardiovascular (CV) events and mortality; thus, they are the preferred treatment to reduce the risk ASCVD and recommended as the first-line treatment by multiple guidelines.
- AHA/ACC Guidelines recommend ezetimibe before PCSK9 inhibitors in patients with ASCVD. Although there is limited evidence supporting the strategy of ezetimibe before PCSK9 inhibitors, guidelines state that ezetimibe is widely available as a generic and has proven safety and tolerability along with CV outcomes data. [1]
- Based on results from the IMPROVE-IT study, ezetimibe has also been shown to modestly improve cardiovascular outcomes. Although, it was studied in a very narrow, high-risk population it is a treatment option in patients with clinical ASCVD or HeFH.
- The addition of ezetimibe to statin therapy typically reduces LDL-C by 15% to 30% in patients with hyperlipidemia.
- AHA/ACC Guidelines state that PCSK9 inhibitors are reasonable in patients with very high risk ASCVD who cannot achieve an LDL or < 70 mg/dL while on a high-intensity statin and ezetimibe.
- PCSK9 inhibitors have 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.

- Treatment with either Praluent (alirocumab) or Repatha (evolocumab) in combination with a statin improved CV outcomes. However, the magnitude of benefit was modest.
- CV outcomes data for Leqvio (inclisiran) is not yet available. The use of medications with proven CV benefits is required prior to coverage of Leqvio (inclisiran), as outlined in the coverage criteria, as the CV benefits of Leqvio (inclisiran) are unknown at this time.
- 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.
- 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 Praluent (alirocumab) 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, most of these patients were able to tolerate statin therapy, thus requiring trials of multiple statins prior to coverage of a PCSK9 inhibitor is warranted.
- 2018 AHA/ACC Guidelines state that in patients with statin-associated side effects that are not severe, it is recommended to reassess and to re-challenge to achieve a maximal LDL-C lowering by modified dosing regimen, an alternate statin or in combination with non-statin therapy.
- PCSK9 inhibitors have not been studied in combination with any other PCSK9 inhibitor or Juxtapid (lomitapide).
- PCSK9 inhibitors appear to be well-tolerated. However, additional long-term studies and clinical experience is needed with Leqvio (inclisiran).
- In late 2018, the manufacturer of Repatha (evolocumab) introduced new NDC's (beginning with 72511) at a significant discount. The previous (legacy) NDC's (beginning with 55513) have been discontinued as of December 31, 2019.

Clinical Efficacy

Praluent (alirocumab)

- The ODYSSEY OUTCOMES study evaluated the impact of Praluent (alirocumab) on cardiovascular outcomes in patients with a history of acute coronary syndrome (ACS) in the past 1 to 12 months. The primary endpoint was the composite of cardiovascular death, MI, stroke, and hospitalization for unstable angina. Patients were randomized to

either Praluent (alirocumab) 75 mg every two weeks or placebo. All patients were on background high-intensity statins or their maximally-tolerated dose of atorvastatin or rosuvastatin.

  * After a median follow-up of 2.8 years, Praluent (alirocumab) reduced the risk of the primary endpoint compared to placebo (9.5% vs. 11.1%, respectively; hazard ratio, 0.85; 95% CI, 0.78 to 0.93; P<0.001). The secondary endpoint of the composite of death from any cause, non-fatal MI, and non-fatal stroke also favored alirocumab compared to placebo (10.3% vs. 11.9%, respectively; hazard ratio 0.86; 95% CI 0.79 to 0.93; P<0.001).

- The body of evidence supports that Praluent (alirocumab) produces substantial reductions in LDL-C. [2 3]
  * The primary endpoint in the majority of Praluent (alirocumab) phase 3 studies was percent change in LDL-C.
  * Among ten placebo- and active controlled phase 3 studies, Praluent (alirocumab) reduced LDL-C by approximately 43 to 61 percent from baseline. The studies included a several populations, including those with HeFH and/or clinical ASCVD. Studies ranged in duration from 12 to 78 weeks. Results were statistically significant versus placebo and versus ezetimibe.
  * In patients with HoFH the mean LDL-C reduction was approximately 36%.[4]

Repatha (evolocumab)

- 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 Repatha (evolocumab) or placebo and all patients were on background high or moderate intensity statin therapy. [5]
  * 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 Repatha (evolocumab) produces substantial reductions in LDL-C. [6]
  * The primary endpoint in the majority of Repatha (evolocumab) phase 3 studies was percent change in LDL-C. Reductions in LDL-C ranged from 54% to 71% in patients with clinical ASCVD or HeFH. [6]
  * In patients with HoFH the mean LDL-C reduction was approximately 31%. [7]

Leqvio (inclisiran)

- The body of evidence supports that Leqvio (inclisiran) produces substantial reductions in LDL-C. [8 9]

    - The primary endpoint in the majority of Leqvio (inclisiran) phase 3 studies was percent change in LDL-C.
    - Reductions in LDL-C ranged from 40% to 51% in patients with clinical ASCVD or HEFH.
- Although the data continues to evolve, CV outcomes data for Leqvio (inclisiran) is not yet available. Of note, Praluent (alirocumab) or Repatha (evolocumab) in combination with a statin resulted in a modest improvement in CV outcomes in trials.
- Several outcomes trials have demonstrated that statins reduce the risks of cardiovascular and cerebrovascular events. [1]
    - 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.
    - Several primary and secondary prevention trials with simvastatin, pravastatin, lovastatin, and atorvastatin consistently demonstrate that reductions in cardiovascular events correlate with LDL-C reduction.[10-12]

Guidelines

ASCVD

- The 2018 American College of Cardiology and American Heart Association (ACC/AHA) treatment guidelines state that PCSK9 inhibitors are reasonable for patients with very high risk ASCVD who cannot achieve an LDL or < 70 mg/dL while on a high-intensity statin and ezetimibe.
    - Very high risk is defined as a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk condition (see *Appendix 8*).
- For patients with ASCVD the first goal is to achieve a 50% or more reduction in LDL-C, but if LDL-C levels remain 70 mg/dL or great additional treatment with ezetimibe is considered reasonable.
- Guidelines acknowledge that the evidence supporting the use of ezetimibe before PCSK9 inhibitors is limited. Although, patients in both PCSK9 inhibitor outcomes studies were permitted to use ezetimibe, very few did. The recommendation placing ezetimibe ahead of PCSK9 inhibitors is primarily due to wide availability as a generic and proven safety and tolerability.
- PCSK9 inhibitors may also be considered in patients with severe primary hypercholesterolemia (e.g., HeFH) with an LDL-C of 100 mg/dL or greater despite maximally tolerated statin and ezetimibe therapy.

HeFH

- 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. 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. [13]

- Although treatment targets are recommended by clinical guidelines, they are based primarily on surrogate endpoints, expert opinion, and studies in patients without familial hypercholesterolemia. [13-15]
- 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. [13]

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. [16]
- Treatment options include Repatha (evolocumab), Praluent (alirocumab), Juxtapid (lomitapide), traditional lipid-lowering medications, and LDL-apheresis.[16] Kynamro (mipomersen), oligonucleotide inhibitor of apolipoprotein B-100 synthesis indicated for HoFH, was discontinued by its manufacturer in 2018.

Statin intolerance

- ODYSSEY ALTERNATIVE was a 24-week study of Praluent (alirocumab) 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. [16]
    * 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 Praluent (alirocumab), ezetimibe, 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 Praluent (alirocumab) 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 re-challenged.
    - 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. [17]
    - 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.
- 2018 AHA/ACC Guidelines state that in patients with statin-associated side effects that are not severe, it is recommended to reassess and to re-challenge to achieve a maximal LDL-C lowering by modified dosing regimen, an alternate statin or in combination with non-statin therapy. Guidelines authors noted that a large majority of patients can tolerate statin re-challenge with an alternative statin or alternative regimen, such as reduced dose or in combination with non-statins.
- 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/

Dosing considerations

- The recommended starting dose for Praluent (alirocumab) is 75 mg administered subcutaneously once every 2 weeks. If the LDL-C response is inadequate, the dose may be increased to the maximum dose of 150 mg administered every 2 weeks. An alternative starting dose of 300 mg every 4 weeks may also be considered.[3]
- The recommended starting dose of Repatha (evolocumab) for patients with HeFH or clinical ASCVD is 140 mg once every 2 weeks or 420 mg once monthly, administered subcutaneously. The recommended starting dose for patients with HoFH is 420 mg once monthly.[6]
- The recommended dose of Leqvio (inclisiran) is 284 mg given subcutaneously as a single injection, repeated at 3 months, then every 6 months thereafter.[18]

Appendix 1: Dutch Lipid Clinic Network criteria [12]	
Criteria	**Points**
Group 1: family history	
First-degree relative with known premature (less than age 55 for males or 65 for females) coronary heart disease *OR* First-degree relative with known LDL cholesterol above 95th percentile	1
First-degree relative with tendon xanthoma and/or corneal Arcus *OR* Children < 18 years with LDL cholesterol above 95th percentile	2
Group 2: clinical history	
Premature coronary heart disease	2
Subject has cerebral or peripheral vascular disease	1
Group 3: physical examination	
(i) Tendon xanthoma	6
(ii) Corneal arcus in a person before age 45	4
Group 4: biochemical results (LDL-C)	
>8.5 mmol/L (>325 mg/dL)	8
5–8.4 mmol/L (251–325 mg/dL)	5
5.0–6.4 mmol/L (191–250 mg/dL)	3
4.0–4.9 mmol/L (155–190 mg/dL)	1
Group 5: molecular genetic testing (DNA analysis)	
(i) Causative mutation shown in the LDLR, APOB, or PCSK9 genes	8
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 [1 20]
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
Severe trauma
HIV
Diabetes mellitus
Major Surgery
History of creatinine kinase elevation
History of pre-existing/unexplained muscle/joint/tendon pain
Genetic factors such as polymorphisms in genes encoding cytochrome P450 isoenzymes or drug transporter
High level of physical activity
Dietary effects (excessive grapefruit or cranberry juice)
Excess alcohol
Drug abuse (cocaine, amphetamines, heroin)

Appendix 4: Examples of Drug-drug interactions that may increase the risk of skeletal muscle effects with High-Intensity Statins
Strong inhibitors of CYP 3A4 (e.g., clarithromycin, itraconazole, protease inhibitors)
Grapefruit Juice
Cyclosporine
Gemfibrozil and other fibrates
Niacin
Colchicine

Appendix 5: Contraindications to Statin Therapy [10 21]
Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels
History of rhabdomyolysis
Hypersensitivity
Nursing Mothers
Pregnancy

Appendix 6: Clinical Atherosclerotic Cardiovascular Disease (ASCVD) [1]
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 [1]		
% LDL- C Lowering	**Statin Name**	**Strength**
Low-intensity: < 30%	Fluvastatin	20 mg, 40 mg
	Lovastatin	10 mg, 20 mg
	Lovastatin ER (Altoprev)	20 mg
	Pitavastatin (Livalo)	1 mg
	Pravastatin	10 mg, 20 mg
	Simvastatin	5 mg, 10 mg
Moderate-intensity: 31% - 49%	Atorvastatin	10 mg, 20 mg
	Fluvastatin ER (Lescol XL)	80 mg
	Lovastatin	40 mg
	Lovastatin ER (Altoprev)	40 mg, 60 mg
	Pitavastatin (Livalo)	2 mg, 4 mg
	Pravastatin	40 mg, 80 mg
	Rosuvastatin	5 mg, 10 mg
	Simvastatin	20 mg, 40 mg
High-intensity: ≥ 50%	Atorvastatin	40 mg, 80 mg
	Rosuvastatin	20 mg, 40 mg

Appendix 8: AHA/ACC Definition of Very-High Risk ASCVD [1]	
Very high risk includes a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions.	
Major ASCVD Events	**High-Risk Conditions**
Recent ACS (in past 12 months)	Age ≥ 65 years
History of MI (other than recent ACS event)	HeFH
History of ischemic stroke	History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event
Symptomatic Peripheral arterial disease (History of claudication with ABI< 0.85, or previous revascularization or amputation)	Diabetes mellitus
	Hypertension
	Chronic Kidney Disease
	Current Smoking
	Persistently elevated LDL-C (≥ 100 mg/dL) despite maximally tolerated statin therapy and ezetimibe
	History of congestive heart failure

Cross References
Genetic Testing for Familial Hypercholesterolemia, Medical Policy Manual, Policy No. 11
Pharmacy Services Medication Policy Manual, Site of Care Review, dru408

Codes	**Number**	**Description**
HCPCS	J1306	Injection, inclisiran (Leqvio), 1 mg

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Revision History

Revision Date	Revision Summary
3/16/2023	No changes to policy criteria with this annual update.
3/18/2022	New policy (effective 6/1/2022). Replaces individual coverage policies for Praluent (alirocumab), dru406 and Repatha (evolocumab), dru407 and includes Leqvio (inclisiran). No change to intent of coverage from previous criteria: limits coverage to confirmed labeled indications with step therapy with low-cost generics. Inclisiran has an additional clinical step with other PCSK9 inhibitors.

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