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Section:	Prescription Drugs	**Effective Date:**	April 1, 2024
Subsection:	Cardiovascular Agents	**Original Policy Date:**	July 31, 2015
Subject:	Praluent	**Page:**	1 of 11

Last Review Date: March 8, 2024

Praluent

Description

Praluent (alirocumab)

Background
Praluent (alirocumab) is a human monoclonal antibody that binds to proprotein convertase subtilisin kexin type 9 (PCSK9). PCSK9 binds to the low-density lipoprotein cholesterol (LDL-C) receptors (LDLR) on the surface of hepatocytes to promote LDLR degradation within the liver. By blocking PCSK9's ability to work, more receptors are available to clear LDL cholesterol from the blood, thereby lowering LDL cholesterol levels (1).

Regulatory Status
FDA-approved indications: Praluent is a PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) inhibitor indicated: (1)

- To reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease.
- As adjunct to diet, alone or in combination with other low-density lipoprotein cholesterol (LDL-C)-lowering therapies, in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce LDL-C.
  As an adjunct to other LDL-C-lowering therapies in adult patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C.

Physicians often measure creatine kinase (CK) in patients about to begin statins or already on statins. CK is an enzyme that leaks out of damaged muscle. Many physicians will not start or continue statins to lower LDL-C in asymptomatic patients with high CK because of concern

regarding possible statin-induced myositis-rhabdomyolysis. High pretreatment CK, predominantly 3 to 5 times the upper normal limit (UNL), should not be an impediment to start or continue statins to lower LDL-C (2).

Spectrum of statin-associated muscle adverse events: (3)

1. Myalgia: unexplained muscle discomfort often described as ‘‘flu-like’’ symptoms with normal CK level. The spectrum of myalgia complaints includes:
    - Muscle aches
    - Muscle soreness
    - Muscle stiffness
    - Muscle tenderness
    - Muscle cramps with or shortly after exercise (not nocturnal cramping)
2. Myopathy: muscle weakness (not attributed to pain and not necessarily associated with elevated CK)
3. Myositis: muscle inflammation
4. Myonecrosis: muscle enzyme elevations or hyperCKemia
    - Mild > 3-fold greater than baseline untreated CK levels or normative upper limit that are adjusted for age, race, and sex
    - Moderate $\geq$ 10-fold greater than untreated baseline CK levels or normative upper limit that are adjusted for age, race, and sex
    - Severe $\geq$ 50-fold above baseline CK levels or normative upper limit that are adjusted for age, race, and sex
5. Myonecrosis with myoglobinuria or acute renal failure (increase in serum creatinine $\geq$ 0.5 mg/dL (clinical rhabdomyolysis)

Statin intolerance is widely defined as not being able to tolerate a registered statin dose, due to side effects such as myalgia-myopathy, myositis, or elevation of serum liver enzyme activities. Statin intolerance has been also described as a clinical syndrome with the following characteristics: (4)

1. The inability to tolerate at least 2 different statins – one statin at the lowest starting average daily dose and the other statin at any dose
2. Intolerance associated with confirmed, intolerable statin-related adverse effect(s) or significant biomarker abnormalities
3. Symptom or biomarker changes resolution or significant improvement upon dose decrease or discontinuation
4. Symptoms or biomarker changes not attributable to established predispositions such as drug-drug interactions and recognized conditions increasing the risk of statin intolerance

The ACC Statin Intolerance Tool guides clinicians through the process of managing and treating patients who report muscle symptoms while on statin therapy. The tool is available for free online at *Tools.ACC.org/StatinIntolerance* or for download in the App stores. Search "ACC Statin Intolerance".

The safety and efficacy of Praluent in pediatric patients less than 18 years of age have not been established (1).

Related policies
Evkeeza, Juxtapid, Leqvio, Nexletol/Nexlizet, Repatha

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Praluent may be considered **medically necessary** if the conditions indicated below are met.

Praluent may be considered **investigational** for all other indications.

Prior-Approval Requirements

Age 18 years of age or older

Diagnoses

Patient must have **ONE** of the following:

1. Homozygous familial hypercholesterolemia (HoFH)

   AND ALL of the following for HoFH:
   a. Confirmed diagnosis by LDL-R DNA Sequencing Test or APOB (hypercholesterolemia) Mutation Analysis
   b. Genetic confirmation of two mutant alleles at the LDLR, Apo-B, PCSK9, ARH adaptor protein 1/LDLRAP1 gene locus
   c. Provided documentation (medical records, laboratory reports) of baseline and/or current LDL-C level ≥ 100 mg/dL in the past 6 months

2. Heterozygous familial hypercholesterolemia (HeFH)

a. Provided documentation (medical records, laboratory reports) drawn LDL-C level ≥ 100 mg/dL in the past 6 months

AND ONE of the following for HeFH:

a. Confirmed diagnosis by LDL-R DNA Sequencing Test or APOB (hypercholesterolemia) Mutation Analysis
b. Dutch Lipid Clinic Network Criteria score > 5
c. Simon-Broome Diagnostic Criteria for definite familial hypercholesterolemia

3. Atherosclerotic cardiovascular disease (ASCVD)
   a. Provided documentation (medical records, laboratory report) of drawn LDL-C level ≥ 70 mg/dL in the past 6 months

   AND ONE of the following for ASCVD:

   a. Patient has had at least **ONE** of the following atherosclerotic cardiovascular disease (ASCVD) or cardiovascular events:
      i. Acute coronary syndrome (ACS)
      ii. Myocardial infarction (MI)
      iii. Stable or unstable angina
      iv. Coronary or other arterial revascularization procedure (such as PTCA, CABG)
      v. Transient ischemic attack (TIA)
      vi. Peripheral arterial disease (PAD) presumed to be of atherosclerotic origin
      vii. Findings from CT angiogram or catheterization consistent with clinical ASCVD
   b. At high risk for atherosclerotic cardiovascular disease (ASCVD) or cardiovascular event based on 10- year risk score used by **ONE** of the following tools:
      i. ASCVD Pooled Cohort Risk Assessment: score ≥ 7.5%
      ii. Framingham Risk Score: score ≥ 20%

AND ALL of the following for **ALL** indications:

1. Patient will be assessed for response (i.e., LDL-C reduction) and adherence to the prescribed lipid lowering regimen after 3 months
2. Documentation of an inadequate treatment response to 3 months of at least **ONE** high intensity statin **OR** patient has an intolerance or contraindication to statin therapy
3. **NO** dual therapy with another Prior Authorization (PA) lipid lowering agent (see Appendix 1)

4. Patient **MUST** have tried the preferred product (Repatha) unless the patient has a valid medical exception (e.g., inadequate treatment response, intolerance, contraindication)

All approved requests are subject to review by a clinical specialist for final validation and coverage determination once all required documentation has been received. Current utilization, including samples, does not guarantee approval of coverage.

Prior – Approval *Renewal* Requirements

Age 18 years of age or older

Diagnoses

Patient must have **ONE** of the following:

1. Homozygous familial hypercholesterolemia (HoFH)
2. Heterozygous familial hypercholesterolemia (HeFH)
3. Atherosclerotic cardiovascular disease (ASCVD)

AND ALL of the following:

a. Patient has had **ONE** of the following:
   i. Percentage reduction of LDL-C level is ≥ 40%, compared to the level immediately prior to starting a PCSK9 inhibitor
   ii. Absolute LDL-C is less than < 100mg/dL
b. Patient will be assessed for adherence to the prescribed lipid lowering regimen
c. **NO** dual therapy with another Prior Authorization (PA) lipid lowering agent (see Appendix 1)
d. Patient **MUST** have tried the preferred product (Repatha) unless the patient has a valid medical exception (e.g., inadequate treatment response, intolerance, contraindication)

All approved requests are subject to review by a clinical specialist for final validation and coverage determination once all required documentation has been received. Current utilization, including samples, does not guarantee approval of coverage.

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy

Atorvastatin (Lipitor) 40 – 80 mg a day **Rosuvastatin (Crestor)** 20 – 40mg a day	**Atorvastatin (Lipitor)** 10 – 20mg a day **Rosuvastatin (Crestor)** 5 - 10mg a day **Simvastatin (Zocor)** 20 - 40mg a day **Pravastatin (Pravachol)** 40 - 80mg a day **Lovastatin (Mevacor)** 40mg a day **Fluvastatin XL (Lescol XL)** 80mg a day **Fluvastatin (Lescol)** 40mg twice a day **Pitavastatin (Livalo)** 2 - 4mg a day	**Simvastatin (Zocor)** 10mg a day **Pravastatin (Pravachol)** 10 - 20mg a day **Lovastatin (Mevacor)** 20mg a day **Fluvastatin (Lescol)** 20 - 40mg a day **Pitavastatin (Livalo)** 1mg a day

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Quantity

Praluent 75mg	6 syringes per 90 days **OR**
Praluent 150mg	6 syringes per 90 days

Duration 12 months

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary
Praluent (alirocumab) is a human monoclonal antibody that binds to proprotein convertase subtilisin kexin type 9 (PCSK9). PCSK9 binds to the low-density lipoprotein cholesterol (LDL-C) receptors (LDLR) on the surface of hepatocytes to promote LDLR degradation within the liver. By blocking PCSK9's ability to work, more receptors are available to clear LDL cholesterol from the blood, thereby lowering LDL cholesterol levels. The safety and efficacy of Praluent in pediatric patients 18 years or less have not been established (1).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use of Praluent while maintaining optimal therapeutic outcomes.

References
1. Praluent [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; April 2021.
2. Glueck CJ et al. Should high creatine kinase discourage the initiation or continuance of statins for the treatment of hypercholesterolemia. *Metab Clin and Expl Jrnl*;2009(58): 233–238.
3. Rosenson R, Baker S, et al. An assessment by the Statin Muscle Safety Task Force: 2014 update. Jrnl Clin Lipid, 2014; 8, S58‑S71.
4. Banach M, Rizzo M, et al. Statin intolerance ‑ an attempt at a unified definition. Position paper from an International Lipid Expert Panel. Arch Med Sci 2015; 11, 1: 1‑23.

Policy History

Date	Action
July 2015	Addition to PA
August 2015	Removal of non-familial hypercholesterolemia and change to Atherosclerotic cardiovascular disease and removal of documented that the patient has primary severe elevations of baseline and/or current LDL-C of ≥ 190 mg/dL and/or history or presence of xanthomas and removal of laboratory report or medical records of triglyceride level greater than 400 mg/dL in the past 30 days. Change the quantity limits to 90 days. Addition of lipidologist and no dual therapy with Juxtapid and Kynamro. Change in the ASVCD score from 7.5% to 15%.

September 2015	Annual Review Addition of Dutch Lipid Clinic Network Criteria score ≥ 8 and Simon-Broome Diagnostic Criteria for definite familial hypercholesterolemia to heterozygous familial hypercholesterolemia. Addition of med chart. Removal of baseline HDL-C level is less than 60 mg/dL, the patient must have at least two of the following or if greater than 60 mg/dL, the patient must have at least three of the following risk factors for coronary artery disease (CAD):Advancing age, Female: 55 years of age or older, Male: 45 years of age or older, Baseline or current LDL-C ≥ 160 mg/dL, family history of premature CAD with onset < 55 years in a first degree male relative, family history of premature CAD with onset < 65 years in a first degree female relative, HDL-C less than 40 mg/dL, hypertension (BP equal to or greater than 140/90 mmHg or on hypertensive medication), polycystic ovary syndrome and change of active liver disease from the contraindications to intolerance section Addition of “Current utilization, including samples, does not guarantee approval of coverage,” to the criteria
December 2015	Annual review
August 2016	Addition of inadequate response to initial therapy and an increase strength is needed and percentage reduction of LDL-C level is greater than or equal to (≥) 20%, compared to the level immediately prior to starting a PCSK9 inhibitor to the renewal section and documentation in the past 60 days for LDL levels Policy number change from 5.16.06 to 5.40.06
September 2016	Annual editorial review and reference update Change in intolerable and persistent (i.e., more than 2 weeks) muscle symptoms (eg., muscle pain, weakness, cramps) with **ALL** of the following- to **ONE** of the following and addition of those terms Change from documentation provided indicated creatinine kinase (CK) levels greater than 10 times upper normal limit and/or rhabdomyolysis with CK levels greater than 10,000 IU/L) – to 5 times and 2,500 IU/L
December 2016	Annual review

September 2017	Annual editorial review and reference update Removal of the following requirements: prescribed or recommended by cardiologist, endocrinologist, or lipidologist. Change to the requirement for intolerable and persistent muscle symptoms and hepatotoxicity from “one high intensity statin and one low or moderate intensity statin with Zetia” to “two trials of different statins with or without Zetia”. Change of ASCVD LDL level from 100 to 70. Change of ASCVD Pooled Cohort Risk Assessment from 15% to 7.5%, change in intolerance to a statin caused by muscle symptoms the requirement of combination of Zetia and change in CK levels from 5 times ULN to 3 times ULN per SME
December 2017	Annual editorial review
July 2018	Change of HeFH Dutch Lipid clinical network score from ≥8 to >5, change of initiation LDL levels from past 60 days to past 90 days, change in initiation approval length from 3 months to 12 months, addition of inadequate response, intolerance, contraindication to statins to all diagnoses for initiation
August 2018	Addition of 150mg to initiation approval, redefined inadequate response to statins
September 2018	Annual review
November 2018	Annual editorial review and reference update. Removal of Kynamro from dual therapy questions
May 2019	Addition of ACC Statin Intolerance App to regulatory status
June 2019	Annual review and reference update
December 2019	Annual review. Addition of requirement to trial preferred product
June 2020	Annual review and reference update
September 2020	Annual review and reference update
March 2021	Addition of requirement: no dual therapy with Nexletol/Nexlizet. Addition of contraindication to statins to include severe allergic reaction to a statin (e.g., anaphylaxis, angioedema, severe rash)
April 2021	Addition of indication: HoFH. Revised dual therapy requirement to include not dual therapy with Evkeeza.
June 2021	Annual review
June 2022	Annual review
September 2022	Annual review. Per SME, revised regulatory status and removed simvastatin 80mg from the statins list

October 2022	Removed required documentation for HoFH and HeFH LDL-R DNA Sequencing Test or APOB Mutation Analysis. Revised initiation LDL-C levels to drawn level in the past 6 months. Removed required documentation for an ASCVD event or high-risk score. Revised requirements for statin inadequate response and intolerances (myalgia, myositis, and hepatotoxicity). Removed required documentation for renewal LDL level
March 2023	Annual editorial review. Revised wording of no dual therapy requirement for consistency and added Appendix 1
March 2024	Annual review

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 8, 2024 and is effective on April 1, 2024.

Appendix 1 - List of PA Lipid Lowering Agents*

Generic Name	Brand Name
alirocumab	Praluent
bempedoic acid	Nexletol
bempedoic acid/ezetimibe	Nexlizet
evolocumab	Repatha
inclisiran	Leqvio
lomitapide	Juxtapid

*Dual therapy with Evkeeza (evinacumab-dgnb) is allowed