Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO001

Description

Alirocumab (Praluent) and evolocumab (Repatha) are subcutaneous Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) inhibitors.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
alirocumab (Praluent)	75 mg/mL pen injector	Heterozygous familial hypercholesterolemia; Atherosclerotic cardiovascular disease	2 mL (2 injections)/28 days	189256, 189258
	150 mg/mL pen injector			189257, 189259
evolocumab (Repatha)	140 mg/mL auto injector; prefilled syringe		2 mL (2 injections)/28 days	1839578, 189578
	420 mg/mL solution cartridge	Heterozygous familial hypercholesterolemia; Homozygous familial hypercholesterolemia; Atherosclerotic cardiovascular disease	3.5 mL (1 injection)/28 days	193637

Initial Evaluation

I. Alirocumab (Praluent) or evolocumab (Repatha) may be considered medically necessary when the following criteria below are met:
   A. Therapy is prescribed by, or in consultation with, a provider specializing in lipid management (e.g., cardiology, lipidology, endocrinology); **AND**
   B. The member has a LDL-cholesterol level greater than or equal to 70 mg/dL while on maximally tolerated statin therapy; **AND**
   C. Therapy with a high intensity statin (greater than or equal to atorvastatin [Lipitor] 40 mg or rosuvastatin (Crestor) 20 mg) for at least an 8 week duration has been ineffective; **AND**
      1. The member will continue statin therapy in combination with alirocumab (Praluent) or evolocumab (Repatha); **OR**

D. There is documentation of statin failure defined by one of the following:
   1. Treatment with maximally tolerated doses of any statin (e.g., simvastatin [Zocor], pravastatin [Pravachol], etc.) was ineffective or contraindicated; **OR**
   2. The patient has not tolerated at least two statin medications as defined by at least one of the following:
      i. CK exceeds 10 times the upper limit of normal
      ii. LFTs exceed 3 times the upper limit of normal
      iii. Severe rhabdomyolysis leading to hospitalization
      iv. Severe muscle weakness inhibiting activities of daily living, employment, or leading to temporary disability

AND

E. A diagnosis of one of the following:
   1. Atherosclerotic cardiovascular disease (ASCVD); AND
      i. Member is 18 years of age or older; **AND**
      ii. Treatment with ezetimibe (Zetia) has been ineffective, contraindicated, or not tolerated; **AND**
      iii. Documentation of clinical atherosclerotic disease via invasive or non-invasive testing (e.g., stress test, imaging); **OR**
      iv. Diagnosis of atherosclerotic disease and primary prevention failure (e.g., member has had a stroke, myocardial infarction);

      OR

   2. **Heterozygous familial hypercholesterolemia**; **AND**
      i. The member is 18 years of age or older; **AND**
      ii. Diagnosis of heterozygous familial hypercholesterolemia is confirmed by one of the following
         a. Genotyping or clinical criteria using either the Simon Broome diagnostic criteria (definite diagnosis classification) or Dutch Lipid Network criteria (score of at least 8)
         b. Physical signs of familial hypocholesteremia (e.g., arcus cornealis, tendon xanthomas, xanthelasma)
         c. Clinical documentation or a DNA mutation analysis supporting the diagnosis of heterozygous familial hypercholesterolemia;

      OR

   3. **Homozygous familial hypercholesterolemia**; **AND**
      i. The member is 13 years of age or older; **AND**
      ii. The request is for evolocumab (Repatha); **AND**
      iii. The member has a history of an untreated LDL-cholesterol level greater than 500 mg/dL with either evidence of heterozygous familial

hypercholesterolemia in both parents or xanthoma before the age of 10; **AND**

iv. Evolocumab (Repatha) will not be used in combination with mipomersen (Kynamro) or lopitamide (Juxtapid);

II. Alirocumab (Praluent) or evolocumab (Repatha) are considered not medically necessary when used for all other conditions, including but not limited to:
   A. Hypercholesterolemia non-familial cause

III. Alirocumab (Praluent) or evolocumab (Repatha) are considered investigational when used for all other conditions, including but not limited to:
   A. ASCVD primary prevention in non-familial hypercholesterolemia

Renewal Evaluation

I. Member has experienced a decrease from baseline LDL-C while on therapy

Supporting Evidence

I. Alirocumab (Praluent) is FDA-approved to reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease; and as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for the treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) to reduce low-density lipoprotein cholesterol (LDL-C).

II. Evolocumab (Repatha) is FDA-approved to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease; and 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) or homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

III. 2017 American Association of Clinical Endocrinologists (AACE) guidelines state statin therapy is recommended as the primary pharmacologic agent to achieve target LDL-C goals on the basis of morbidity and mortality outcome trials. Additionally, guidelines state PCSK9 inhibitors should be considered in individuals with clinical cardiovascular disease who are unable to reach LDL-C/non-HDL-C goals with maximally tolerated statin therapy. They should not be used as monotherapy except in statin-intolerant individuals.

IV. Seventy to ninety percent of patients are able to tolerate an alternate long-term statin. In clinical practice, 10-25% of patients have musculoskeletal adverse events associated with statin use; however, several studies have determined that the majority of patients with statin-

associated muscle symptoms are able to tolerate subsequent statin therapy with modified dosing regimens.

V. 2011 National Lipid Association (NLA) familial hypercholesterolemia guidelines define therapy as ineffective as inability to achieve a LDL-C of less than 70 mg/dL with treatment in atherosclerotic cardiovascular disease.

VI. **Atherosclerotic cardiovascular disease (ASCVD)**: 2018 American Heart Association/American College of Cardiology (AHA/ACC) Cholesterol Guidelines recommend patients with clinical ASCVD reduce LDL-C with high-intensity statin therapy or maximally tolerated statin therapy. In patients with clinical ASCVD who are judged to be very high risk and considered for PCSK9 inhibitor therapy, maximally tolerated LDL-C lowering therapy should include maximally tolerated statin therapy and ezetimibe (very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions).

- 2017 American College of Cardiology (ACC) Recommendations for Non-Statin Therapy recommends consideration of adding ezetimibe first in patients that are statin intolerant with clinical ASCVD, may consider a bile acid sequestrant as an alternative if ezetimibe intolerant and triglycerides <300 mg/dL.
- Per Schmidt et al. Cochrane Review, "in comparisons of PCSK9 inhibitors versus no PCSK9 inhibitors, current evidence suggests that PCSK9 inhibitors decrease CVD incidence without affecting the incidence of all-cause mortality. In comparisons of PCSK9 inhibitors versus alternative (more established) treatments such as statins or ezetimibe, high-quality evidence is lacking. Differences in risk between people treated with and without PCKS9 inhibitors suggest the absolute treatment benefit will likely be modest (e.g. < 1% change in risk)."

VII. **Heterozygous familial hypercholesterolemia**: The presence of tendon xanthoma is a genetically modulated clinical syndrome of familial hypercholesterolemia. In addition, DNA testing can be used to diagnose familial hypercholesterolemia functional mutations. In clinical trials, enrolled patients with heterozygous familial hypercholesterolemia were diagnosed either by genotyping or clinical criteria ("definite FH" using either the Simon Broome or Dutch Lipid Network).

Simon Broome Familial Hypercholesterolemia Register diagnostic criteria for familial hypercholesterolemia	
Criteria	**Description**
A	Total cholesterol concentration above 7.5 mmol/liter (290 mg/dL) in adults or a total cholesterol concentration above 6.7 mmol/liter (259 mg/dL) in children aged less than 16 years, or
	Low density lipoprotein cholesterol concentration above 4.9 mmol/liter (189 mg/dL) in adults or above 4.0 mmol/liter (155 mg/dL) in children
B	Tendinous xanthomata in the patient or a first-degree relative
C	DNA-based evidence of mutation in the *LDLR, PCSK9,* or *APOB* gene

D	Family history of myocardial infarction before age 50 years in a second-degree relative or before age 60 years in a first-degree relative
E	Family history of myocardial infarction before age 50 years in a second-degree relative or before age 60 years in a first-degree relative
A "definite" FH diagnosis requires either criteria a and b, or criterion c. A "probable" FH diagnosis requires either criteria a and d, or criteria a and e.	

Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolaemia	
Criteria	**Points**
Family history	
• First-degree relative with known premature (men: <55 years; women: <60 years) coronary or vascular disease, or • First-degree relative with known LDL-C above the 95th percentile	1
• First-degree relative with tendinous xanthomata and/or arcus cornealis, or • Children <18 years of age with LDL-C above the 95th percentile	2
Clinical History	
• Patient with premature (men: <55 years; women: <60 years) coronary artery disease	2
• Patient with premature (men: <55 years; women: <60 years) cerebral or peripheral vascular disease	1
Physical examination	
• Tendinous xanthomata	6
• Arcus cornealis before age 45 years	4
LDL-C levels	
• LDL-C ≥8.5 mmol/L (325 mg/dL)	8
• LDL-C 6.5-8.4 mmol/L (251-325 mg/dL)	5
• LDL-C 5.0-6.4 mmol/L (191-250 mg/dL)	3
• LDL-C 4.0-4.9 mmol/L (155-190 mg/dL)	1
DNA analysis	
• Functional mutation in the LDLR, apoB, or PCSK9 gene	8
Choose only one score per group, the highest applicable diagnosis (diagnosis is based on the total number of points obtained) • A "definite" FH diagnosis requires >8 points • A "probable" FH diagnosis requires 6-8 points • A "possible" FH diagnosis requires 3-5 points	

- Using DNA testing, patients with familial hypercholesterolemia (FH) have been identified as generally having a functional mutation of one of three genes: *LDLR, PCSK9,* or *APOB* gene. Mutations in these three genes can be detected in about 80 percent of patients with the definite FH clinical syndrome.

- 2017 AACE guidelines state PCSK9 inhibitors should be considered for use in combination with statin therapy for LDL-C lowering in individuals with FH.

VIII. **Homozygous familial hypercholesterolemia (HoFH):** Only evolocumab (Repatha) is FDA-approved in the setting of HoFH and includes patients ages 13 and older. In one multi-center, double-blind, randomized, placebo-controlled trial (TESLA Part B), Repatha was studied in patients greater than or equal to 13 years of age with homozygous familial hypercholesterolemia. Patients in the clinical trial had familial hypercholesterolaemia diagnosed either by genetic analysis or clinical criteria (history of an untreated LDL cholesterol concentration >13 mmol/L (500 mg/dL) plus either xanthoma before 10 years of age or evidence of heterozygous familial hypercholesterolaemia in both parents.

- Use of evolocumab (Repatha) with mipomersen (Kynamro) or lopitamide (Juxtapid) has not been studied and the efficacy and safety is unknown. Concurrent use is considered experimental and investigational.

Investigational or Not Medically Necessary Uses

I. Primary hypercholesterolemia
   A. The use of statins, including in patients considered to be high risk, is recommended as first line therapy by multiple guidelines.
   B. 2018 AHA/ACC guidelines state “at any given price, the economic value of PCSK9 inhibitors will be improved by restricting their use to patients at very high-risk of ASCVD events”.

II. ASCVD primary prevention in non-familial hypercholesterolemia
   A. Trials in prevention of cardiovascular events have occurred in the established cardiovascular disease population (secondary prevention). PCSK9 inhibitors have not been adequately evaluated in primary prevention in patients without familial hypercholesterolemia. Applicability of results to primary prevention is limited.
   B. Per 2018 AHA/ACC guidelines, among patients with FH without evidence of clinical ASCVD taking maximally tolerated statin and ezetimibe therapy, PCSK9 inhibitors provide uncertain value at mid-2018 U.S. list prices. Economic models have not been produced for primary prevention in non-familial hypercholesterolemia.

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Policy Implementation/Update:

Date Created	August 2015
Date Effective	March 2016
Last Updated	June 2019
Last Reviewed	02/2016, 11/2017, 6/2018

Action and Summary of Changes	**Date**
Updated to policy format. Added requirement of ezetimibe trial and failure in ASCVD.	06/2019
Removed alternate statin dosing strategies in patients who are statin intolerant. Decreased LDL cutoff to >70 for all indications. Increased initial authorization to 12 months. Removed requirement to try and fail statin plus Zetia combination therapy. Removed DNA mutation analysis confirming homozygous familial hypercholesterolemia diagnosis. Required trial and failure of high intensity statin for a minimum of 8 week duration. Updated renewal criteria to assess overall reduction in LDL rather than specific percent reduction.	06/2018
Addition of Repatha 420mg/3.5mL pushtronex system to the approval language.	11/2018
Removed triple step therapy with an additional LDL lowering agent. Increased initial authorization to 6 months.	02/2016