Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors
EOCCO POLICY

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	Indication	Dosage Form	Quantity Limit
alirocumab (Praluent)	Heterozygous familial hypercholesterolemia; Homozygous familial hypercholesterolemia; Atherosclerotic cardiovascular disease; Non-familial hypercholesterolemia	75 mg/mL pen injector	2 mL (2 pens)/28 days
		150 mg/mL pen injector	
evolocumab (Repatha)		140 mg/mL auto injector pen; prefilled syringe	2 mL (2 pens; PFS)/28 days
		420 mg/mL solution cartridge	3.5 mL (1 cartridge)/28 days

Initial Evaluation

I. **Alirocumab (Praluent) or evolocumab (Repatha)** may be considered medically necessary when the following criteria below are met:
   A. The member has an LDL-C level greater than, or equal to, 70 mg/dL while on maximally tolerated statin therapy; **AND**
   B. If the request is for alirocumab (Praluent), treatment with evolocumab (Repatha) has been ineffective, not tolerated, or contraindicated; **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. Provider attestation that there is clinical documentation of statin failure defined by <u>one</u> 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 member 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 muscle weakness inhibiting activities of daily living, employment, or leading to temporary disability; **OR**
3. The member experienced severe rhabdomyolysis after the use of at least one statin; **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. Attestation that there is clinical documentation supporting a diagnosis clinical atherosclerotic disease via invasive or non- invasive testing (e.g., stress test, imaging); **OR**
    iii. 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 10 years of age or older; **OR**
        a. The member is 8 years of age or older and the request is for alirocumab (Praluent); **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 greater than 8)
        b. Attestation that there is clinical documentation or a DNA mutation analysis supporting the diagnosis of heterozygous familial hypercholesterolemia; **OR**
3. **Homozygous familial hypercholesterolemia**; **AND**
    i. The member is 18 years of age or older; **OR**
        a. The member is 10 years of age or older and the request is for evolocumab (Repatha); **AND**
    ii. 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; **OR**
        a. Attestation that there is documentation of DNA mutation analysis supporting the diagnosis of homozygous familial hypercholesterolemia (e.g, *LDLR, APOB, PSCK9, LDLRAP1*); **AND**

iii. Evolocumab (Repatha) or alirocumab (Praluent) will not be used in combination with lopitamide (Juxtapid)

4. **Non-familial hypercholesterolemia; AND**
   i. The member is 18 years of age or older; **AND**
   ii. The member has a history of an untreated LDL-C level greater than, or equal to, 190 mg/dL; **AND**
   iii. Treatment with ezetimibe (Zetia) has been ineffective, contraindicated, or not tolerated; **AND**
   iv. The member is unable to achieve ≥50% LDL-C reduction and LDL-C <100 mg/dL or non-HDL-C <130 mg/dL on maximally tolerated cholesterol lowering therapy; **AND**
   v. Provider attestation hypercholesterolemia is not due to a reversible/untreated secondary cause (e.g. hypothyroidism, nephrotic syndrome, primary biliary cholangitis)

II. 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 with untreated LDL-C < 190 mg/dL

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has experienced a decrease from baseline LDL-C while on therapy; **AND**
IV. If the request is for alirocumab (Praluent), treatment with evolocumab (Repatha) has been ineffective, not tolerated, or contraindicated

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 patients 10 years and older with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) or homozygous familial

hypercholesterolemia who require additional lowering of 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 patients 10 years and older with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) or homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

III. The 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. The 2011 National Lipid Association (NLA) familial hypercholesterolemia guidelines define ineffective therapy as inability to achieve an 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).

- The 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 and may consider a bile acid sequestrant as an alternative if ezetimibe intolerant and triglycerides <300 mg/dL.
- Ezetimibe is a clinically appropriate and cost-effective alternative to PSCK9 inhibitors in scenarios where addition of ezetimibe would be expected to bring LDL-C levels to a patient specific LDL-C goal. In patients with ASCVD, the 2018 AHA/ACC Cholesterol Guidelines recommend achieving a ≥50% reduction in LDL-C levels and an LDL-C goal of <70mg/dL. The 2021 European Society of Cardiology Guidelines recommend lipid-lowering treatment with an ultimate goal of <55mg/dL and a ≥50% reduction of LDL-

C from baseline. Depending on specific risk factors, providers may choose different LDL-C goals for their patients. Ezetimibe is cited to lower LDL-C by 15-20% when used by itself or in combination with a statin. Therefore, information about patient's specific LDL-C goals and concomitant cholesterol lowering therapies is required to estimate overall LDL-C lowering effect and assess appropriateness of treatment with ezetimibe.

- 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. Insight from cardiology specialists indicate that diagnosis of clinical ASCVD in the absence of a cardiovascular event can be achieved by angiography, ischemia on stress test, or stenosis of 50% or more using other imaging techniques. While evidence of coronary calcification on CTA (calcium score >1) is indicative of high-risk of developing ASCVD, this number should be integrated into the member's clinical profile to determine individual patient risk and treatment but should not necessarily be used alone for the purposes of clinical diagnosis.

VIII. **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 (190-250 mg/dL)	3
• LDL-C 4.0-4.9 mmol/L (155-189 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.
- The 2017 AACE guidelines state PCSK9 inhibitors should be considered for use in combination with statin therapy for LDL-C lowering in individuals with FH.

IX. **Homozygous familial hypercholesterolemia (HoFH):** Evolocumab (Repatha) and alirocumab (Praluent) are FDA-approved in the setting of HoFH and includes patients ages 13 and older (Repatha) or 18 and older (Praluent). Evocolumab (Repatha) was studied in one multi-center, double-blind, randomized, placebo-controlled trial (TESLA Part B) in patients greater than, or equal to, 13 years of age with homozygous familial hypercholesterolemia. Patients in the clinical trial had familial hypercholesterolemia 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 hypercholesterolemia in both parents. Alirocumab (Praluent) was studied in one randomized, double-blind, placebo-controlled, parallel-group, phase 3 study (ODYSSEY HoFH) in patients 18 years of age or older with homozygous familial hypercholesterolemia. Patients in the clinical trial had a diagnosis of familial hypercholesterolemia confirmed in the patient's medical history by clinical diagnosis or by genotyping. The genotyping results from this study found patients had mutations in the *LDLR, LDLRAP1, PCSKP,* or *APOB* genes.

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

X. **Non-familial hypercholesterolemia**

- The use of statins, including in patients considered to be high risk, is recommended as first line therapy by multiple guidelines. Statins have pleiotropic effects, which involves improvement of endothelial function, decreasing oxidative stress and inflammation, enhancing stability of atherosclerotic plaques, and inhibiting thrombogenic response. These pleiotropic effects have been hypothesized for PCSK9 inhibitors in preclinical studies but have not yet been established.
- Long term risk of ASCVD or CHD (defined as CHD death or non-fatal MI) in adults with familial hypercholesterolemia phenotype (defined as LDL-C levels ≥ 190 mg/dL, irrespective of genetic confirmation of true familial hyperlipidemia or family history of cardiovascular disease) was evaluated using pooled data from 6 large epidemiological studies consisting of 68,565 patients between 20 and 79 years old. The reference group were patients with LDL-C <130 mg/dL. Sensitivity analyses were utilized for patients with LDL-C levels ≥ 190 mg/dL and positive family history. Statin or other hyperlipidemia medications were not specifically reported out within the trial, but it was noted that the vast majority of the data were collected before widespread use of statins. Rate of cholesterol treatment at baseline were very low, between 0% and 4.4% for the different analysis arms, with slightly higher but statistically significant usage within the ≥ 190 mg/dL population for certain age groups. Baseline characteristics were largely the same, but there were statistically significant higher proportion of smokers and hypertension treatment at baseline in

the LDL ≥ 190 mg/dL. Overall, adjusted for age, race, BMI, DM, smoking, blood pressure treatment, patients with LDL ≥ 190 mg/dL were at 1.3 (95% CI 1.0-1.7) to 5.0 (95% CI 1.1-21.7) times higher risk of CHD and up to 4.1x higher total risk of ASCVD (HR 4.1 (95% CI, 1.2-13.4). Hazard ratios for CHD risk decreased with age but was significant in all age groups except those between 70-79 years old (HR 1.3; 95% CI 1.3 (1.0-1.7)). This study demonstrated that irrespective of genetic confirmation of familial hyperlipidemia or family history of cardiovascular disease, patients with LDL-C levels ≥ 190 mg/dL, were at 2-5x higher risk of CHD, and up to 4x higher risk for ASCVD.

- Khera et al. assessed the relationship between severe hypercholesterolemia (defined as untreated LDL-C ≥190 mg/dl) and CAD risks, found that among 20,485 CAD-free and prospective cohort participants, 1,386 (6.7%) had LDL ≥ 190 mg/dL, and of those, gene sequencing only identified 24 patients (1.7%) with FH mutation. Compared to reference group of LDL <130 mg/dl and no mutation, those with LDL ≥190 mg/dL and had no FH mutation were at 6x higher risk for CAD (OR 6.0; 95% CI 5.2-6.9), and those with ≥190 mg/dL and FH mutation were at 22x higher risk (OR 22.3; 95% CI (10.7-53.2)). This data suggests that even patients without confirmed genetic familial hypercholesterolemia but severe untreated LDL-C ≥ 190 mg/dL are at significantly higher risk of developing CAD.
- A systematic review and meta-analysis containing a total of 312,175 patients from 49 trials among different therapeutic interventions demonstrated a relative risk for major vascular events per 1-mmol/L (38.7 mg/dL) reduction in LDL-c level was 0.77 (95% CI, 0.71-0.84; p<0.001) for statins and 0.75 (95% CI, 0.66-0.86; P=0.002) for non-statin therapies. The meta-analysis consisted of trials assessing statins (25), ezetimibe (1), fibrates (9), niacin (3), CETP inhibitors (3), diet (4), bile acid sequestrants (2), ileal bypass (1), and PCSK9-inhibiotrs (2). Primary prevention trials achieved 1.5% (95% CI, 0.5%-2.6%) lower event rate of major coronary events per each 38.7 mg/dL LDL-C level reduction (p=0.008) and secondary prevention trials achieved 4.6% (95% CI, 2.9%-6.4%) lower event rate per 38.7 mg/dL LDL-C level reduction (p<0.001). Major vascular events included: cardiovascular death, acute MI or other ACS, coronary revascularization, or stroke. The two PCSK9 inhibitor studies (ODYSSEY Long Term and OSLER) consisted of 6,808 patients and demonstrated a 0.49 relative risk (95% CI, 0.34-0.71) between treatment and control groups for each 38.7 mg/dL reduction in LDL. ODYSSEY and OSLER contained both primary and secondary prevention patients in conjunction with evidence that PCSK-9 inhibitors
- OSLER-1 and OSLER-2 were longer-term Open-Label extension trials for five Phase 2 (MENDEL-1, LAPLACE-TIMI 57, GAUSS-1, RUTHERFORD-1, YUKAWA-1) and seven Phase 3 trials (MENDEL-2, LAPLACE-2, GAUSS-2, RUTHERFORD-2, DECSCARTES, THOMAS-1, THOMAS-2) evaluating evolocumab. OSLER demonstrated a 1.23%

absolute risk reduction of cardiovascular events (i.e. death, MI, unstable angina requiring hospitalization, coronary revascularization, stroke, transient ischemic attack, heart failure hospitalization) between evolocumab plus standard of care group vs standard of care alone group at 1 year (0.95% vs 2.18%, respectively). With regards to LDL-C lowering, evolocumab demonstrated greater than 70 mg/dL absolute reduction in LDL-C by 12 weeks, and approximately a 60% reduction in LDL-C. This reduction in LDL-C was sustained at every time point through 48 weeks. About 10% of patients enrolled in OSLER had known familial hypercholesterolemia, 20% had coronary artery disease, 24% had family history of premature coronary artery disease, and 9% had cerebrovascular or peripheral artery disease. The patient characteristics of these trials demonstrate that statistically significant absolute risk reduction of cardiovascular events can be achieved even when the majority of patients did not have familial hypercholesterolemia or coronary artery disease at baseline.

- The DESCARTES trial, a 52-week randomized placebo-controlled trial containing 901 adult patients between 18 and 75 years old with LDL cholesterol of ≥75mg/dL and fasting triglyceride of ≤400 mg/dL. After a 4-week run-in period, patients with CHD or CHD risk equivalent and LDL < 100 mg/dL, or no CHD or CHD risk equivalent and LDL <130 mg/dL, or on maximal background therapy were randomized 2:1 to evolocumab 420mg SC Q4W or Placebo between 4 different treatment arms; patients treated with diet alone, patients treated with diet and atorvastatin 10 mg, patients treated with diet and atorvastatin 80mg, and patients treated with diet, atorvastatin 80mg and ezetimibe 10mg. At baseline, 15.1% of patients had coronary artery disease, but prevalence of familial hyperlipidemia was not reported. Given the mean baseline LDL-C was between 94.6 to 119.8 mg/dL, the proportion of patients with familial hyperlipidemia is expected to be relatively low compared to the overall study population. Overall, the DESCARTES study demonstrated a statistically significant -57.0% ± 2.1% mean change from baseline in LDL between evolocumab and placebo group at 52 weeks. Eighty-two point 3 percent of patients achieved LDL of <70 mg/dL at 52 weeks, compared to 6.5% for the placebo group. Roughly 1/3rd of the patients that achieved LDL <70mg/dL while on placebo at 52 weeks were from the diet plus 80mg atorvastatin plus ezetimibe 10mg arm. Within this treatment arm, there was a -48.5± 5.2 mean difference in percent change from baseline LDL cholesterol at 52 weeks of treatment. The DESCARTES trial demonstrated that even while on max dose high intensity statin and ezetimibe, the addition of a PCSK9-inhibitor can still achieve significant reduction in LDL cholesterol levels from baseline.
- Per 2022 ACC Expert Consensus Decision Pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic

cardiovascular disease risk, there is a pathway for consideration of PCSK9 inhibitors for adults without clinical ASCVD and with baseline LDL-C ≥190 mg/dL not due to secondary causes who are taking statin therapy for primary prevention. The panel recommends the addition of ezetimibe and/or PCSK9 inhibitors to maximally tolerated statin therapy if LDL-C reduction of ≥50% LDL-C reduction and LDL-C <100 mg/dL or non-HDL-C <130 mg/dL is not achieved.

- Secondary causes of hypercholesterolemia are caused by medications, substances, and medical conditions leading to elevated levels of LDL and other lipids. Hypothyroidism, nephrotic syndrome, primary biliary cholangitis, and diabetes have the most supporting evidence to suggest a link between the condition and secondary elevation of lipid levels, specifically LDL cholesterol. In line with the recommendations from the 2018 ACC/AHA guidelines and 2022 ACC Expert Consensus recommendations, LDL elevation due to secondary causes does not warrant the same level of consideration for treatment with the exception of diabetes. Although diabetes is an established secondary cause of hypercholesterolemia, the condition is also a significant risk factor that warrants additional and more intensive lipid lowering to reduce the risk of atherosclerosis.
- Safety and efficacy of PCSK9 inhibitors, specifically Repatha (evolocumab) has not been established in non-familial hyperlipidemia pediatric patients.

Investigational or Not Medically Necessary Uses

I. ASCVD Primary prevention non-familial hypercholesterolemia with LDL-C < 190 mg/dL
   A. Currently, there is no established data to support the use of PCSK-9 inhibitors in the primary prevention setting for patients with an LDL-C level below 190 mg/dL. In accordance with the 2022 ACC Expert Consensus statement and 2023 American Diabetes Association Standards of Care in Diabetes Guidelines, in the absence of ASCVD or baseline LDL-C 190 mg/dL, PCSK-9 inhibitors do not have an established, evidence-based role for primary prevention of ASCVD. For patients without ASCVD and have and LDL-C of 70-189 mg/dL, the ACC Expert writing committee does not routinely recommend PCSK9 inhibitors given limited efficacy data and low cost-effectiveness in primary prevention patients on statin therapy.
   B. According the 2018 AHA/ACC clinical guidelines, patients with an LDL-C of ≥ 190 mg/dL in primary prevention or secondary prevention are at a higher risk of future ASCVD events, and do not require a risk assessment before starting lipid lowering therapy. Patients with a baseline LDL-C between 70 mg/dL and 189 mg/dL are at lower risk of future ASCVD events, and ASCVD risk assessment is warranted before initiation of therapy. The use of statin is recommended as the first line treatment option for these patients.

C. Within the 2022 ACC Expert Consensus statement, an LDL-C cutoff of 190 mg/dL is utilized direct management to PCSK9 inhibitors. For adults with possible statin intolerance without clinical ASCVD and LDL-C <190 mg/dL, ezetimibe is considered the first line non-statin therapy, and bile acid sequestrants are considered second-line therapy. PCSK9 inhibitors are not included in this recommendation pathway unless than member has clinical ASCVD or an LDL-C > 190mg/dL. Standard LDL-C scales and lipid panels considers an LDL of 160-189 mg/dL as high, and LDL of ≥ 190 mg/dL as very high or severely elevated. An LDL of 160-189 mg/dL in primary hypercholesterolemia is considered a risk-enhancing factor for clinician-patient risk discussion.
A 14,570-participant cohort study presented at the American Heart Association 2021 Scientific Sessions compared the risk of major adverse cardiovascular events (MACE) in the next 10 years in patients between 20-39 years old with an LDL-C of 160-189 mg/dL to patients with an LDL-C of less than 160 mg/dL. Results showed that the risk of MACE were not significantly different between the two groups (OR. 1.28 [95% CI, 0.94-1.74; p <0.115). MACE was defined as all-cause death, MI, ischemic stroke, heart failure hospitalization, and peripheral vascular disease. While there was not a comparison cohort of patients with LDL-C > 190mg/dL in this study, the result is in line with the understanding that patients with an LDL-C of <190 mg/dL are not at a significantly higher risk for ASCVD and major adverse cardiovascular events, even if their LDL-C is elevated at 160-189 mg/dL.

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Policy Implementation/Update:

Action and Summary of Changes	Date
Updated to include Praluent age expansion in pediatric patients aged 8 years and older with heterozygous familial hypercholesterolemia (HeFH). Removed specialist prescribing requirement.	07/2024
Addition of non-familial hypercholesterolemia criteria and supporting evidence. Removed not medically necessary criteria for Hypercholesterolemia non-familial cause indication, and added ASCVD primary prevention non-familial hypercholesterolemia with LDL-C 190mg/dl to experimental and investigational criteria. Minor formatting changes.	02/2023
Updated to allow provider attestation in HoFH DNA mutation analysis. Require history with only one statin in the setting of previous rhabdomyolysis.	01/2023
Removed ezetimibe step criteria for ASCVD. Included trial of Repatha prior to Praluent within initial and renewal criteria.	12/2022
Added criteria allowing a path to coverage in scenarios where ezetimibe would not be expected to bring LDL-C levels to a desired LDL-C goal. Updated supporting evidence.	08/2022
Updated to include age expansion in pediatric patients aged 10 years and older with heterozygous familial hypercholesterolemia (HeFH) or homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C	02/2022
Added new FDA-approved indication of HoFH for Praluent. Updated diagnosis confirmation requirements for HeFH and HoFH to align with current guidelines. Removed statement around combination use with Kynamro as product has been discontinued. Update to supporting evidence.	04/2021
Review. Update to supporting evidence	12/2020
Updated to policy format. Added requirement of ezetimibe trial and failure in ASCVD.	06/2019
Addition of Repatha 420mg/3.5mL pushtronex system to the approval language.	11/2018
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
Previous review	11/2017
Removed triple step therapy with an additional LDL lowering agent. Increased initial authorization to 6 months.	02/2016
Criteria created	08/2015