Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors

- Praluent (alirocumab)
- Repatha (evolocumab)
- Leqvio (inclisiran)

Summary

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, including Praluent (alirocumab), Repatha (evolocumab), and Leqvio (inclisiran), are FDA-approved medications used in conjunction with diet and maximally tolerated statin therapy to lower LDL cholesterol in those with certain conditions, including, as adjunct therapy for:

1. Atherosclerotic cardiovascular disease (ASCVD), to reduce risk of major cardiovascular events including myocardial infarction, stroke, unstable angina requiring hospitalization, coronary revascularization, and cardiovascular death in adults with established ASCVD.
2. Heterozygous familial hypercholesterolemia (HeFH).
3. Homozygous familial hypercholesterolemia (HoFH).
4. Hypercholesterolemia or hyperlipidemia.

Praluent and Repatha are monoclonal antibodies that bind to and inhibit PCSK9, enhancing the number of LDL receptors available to clear LDL cholesterol. Leqvio uses siRNA technology to inhibit PCSK9 production. All are administered subcutaneously, but Leqvio (inclisiran) must be given by a healthcare professional.

For the latest clinical practice guidelines, the ACC/AHA recommendations should be reviewed, accessible via the ACC website at https://www.acc.org/guidelines. Other sources of clinical practice guidelines include the American Association of Clinical Endocrinology and the National Institute for Health and Care Excellence, which may differ in some recommendations. Please see Appendix A, Table 1 for a list of The Plan's preferred and non-preffered PCSK9 inhibitors.

Definitions

"Atherosclerotic Cardiovascular Disease (ASCVD)" is a term used to describe conditions that are caused by atherosclerosis, a disease where plaque builds up inside the arteries. Plaque is made up of fat, cholesterol, calcium, and other substances found in the blood. Over time, the plaque hardens and can narrow the arteries, limiting the flow of oxygen-rich blood to the body's organs and tissues. This can lead to different cardiovascular conditions. Examples of ASCVD include:

- Coronary Artery Disease (CAD): This occurs when the coronary arteries, which supply blood to the heart, become hardened and narrowed due to plaque buildup. This can lead to chest pain (angina), a heart attack (myocardial infarction), or heart failure.
- Carotid Artery Disease: The carotid arteries in the neck supply blood to the brain. Atherosclerosis in these arteries can lead to transient ischemic attacks (mini-strokes) or strokes.

- Peripheral Arterial Disease (PAD): This occurs when atherosclerosis affects the arteries that carry blood to the arms and legs. PAD can cause pain and fatigue, typically in the legs, and can increase the risk of infection and amputation.
- Aortic Atherosclerosis and Aortic Aneurysm: The aorta, the largest artery in the body, can also be affected by atherosclerosis. This can lead to an aortic aneurysm, where a section of the aorta becomes overly large and may rupture, a life-threatening event.

"Cholesterol" is a waxy, fat-like substance produced in the body and essential for various biological functions such as forming cell membranes, producing certain hormones, and synthesizing vitamin D. However, excessive amounts can lead to plaque formation in arteries.

"Documentation" refers to written information, including but not limited to:

- Up-to-date chart notes, relevant test results, and/or relevant imaging reports to support diagnoses; or
- Prescription claims records, and/or prescription receipts to support prior trials of formulary alternatives.

"Ezetimibe" is a cholesterol-lowering medication that works by blocking the absorption of dietary cholesterol in the small intestine, which in turn decreases total and LDL cholesterol levels in the bloodstream.

"Heterozygous Familial Hypercholesterolemia (HeFH)" is a genetic disorder, inherited from one parent, that results in high levels of LDL cholesterol, often leading to premature atherosclerotic cardiovascular disease.

"Homozygous Familial Hypercholesterolemia (HoFH)" is a more severe form of familial hypercholesterolemia, inherited from both parents, that leads to extremely high LDL cholesterol levels. This can cause serious cardiovascular complications at a young age.

"Hypercholesterolemia" or "Hyperlipidemia" is a condition characterized by high levels of lipids (fats) in the blood, including cholesterol and triglycerides.

"Low-Density Lipoprotein Cholesterol (LDL-C)" is often referred to as "bad" cholesterol, LDL-C transports cholesterol to the cells throughout the body. High levels of LDL-C can lead to a buildup of cholesterol in arteries, contributing to atherosclerosis.

"No evidence of" indicates that the reviewer has not identified any records of the specified item or condition within the submitted materials or claims history. In the absence of such evidence, the member is considered eligible. If any evidence of the item or condition is present upon review of the request, the member does not qualify.

"Proprotein Convertase Subtilisin Kexin 9 (PCSK9)" is a protein that regulates the number of LDL receptors on the surface of cells. Inhibitors of PCSK9 increase the number of LDL receptors available to clear LDL cholesterol from the bloodstream.

"Ribonucleic Acid (RNA)" is a single-stranded molecule involved in protein synthesis, gene regulation, and as the genetic material of some viruses. RNA plays a significant role in transmitting genetic information and cellular functioning.

"[s]" indicates state mandates may apply.

"Small Interfering RNA (siRNA)" is a type of RNA molecule that interferes with the expression of specific genes with complementary nucleotide sequences by degrading mRNA after transcription, preventing translation into protein. Inclisiran (Leqvio) uses siRNA technology to inhibit the production of PCSK9 protein, leading to lower LDL cholesterol levels.

"Statins" refers to the class of medications, including drugs like atorvastatin and lovastatin, that lower cholesterol levels by inhibiting an enzyme (HMG-CoA reductase) involved in cholesterol synthesis in the liver.

"Xanthoma" is a skin condition characterized by the deposition of fat beneath the skin's surface, leading to the formation of yellowish growths or bumps. Xanthomas are often indicative of underlying lipid disorders, including high cholesterol or triglyceride levels.

Medical Necessity Criteria for Clinical Review

General Medical Necessity Criteria

The Plan considers Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors medically necessary when ALL the following are met:

1. The medication is being prescribed by or in consultation with an endocrinologist, cardiologist, lipid specialist or someone who specializes, or who has extensive experience, in familial hypercholesterolemia or atherosclerotic cardiovascular disease; *AND*
2. The medication being requested meets BOTH of the following:
    a. Is being prescribed for an FDA-approved or compendia supported indication*; and*
    b. Is age-appropriate for the member based on FDA approval or is supported by evidence-based compendia, such as:
        i. Primary hyperlipidemia/ASCVD: ≥18 years (all agents); *or*
        ii. HeFH: ≥8 years (Praluent), ≥10 years (Repatha), ≥18 years (Leqvio); *or*
        iii. HoFH: ≥18 years (Praluent), ≥10 years (Repatha); [*Not indicated for Leqvio*]*; AND*

3. IF the request is for a non-preferred product (i.e., Leqvio, Repatha), the member is unable to use, or has tried and failed the Plan's preferred product (i.e., Praluent) as age and indication appropriate,[s] *AND*
4. The requested medication will not be used concomitantly with other PCSK9 inhibitors (i.e., must discontinue current therapy before initiating different agent)*; AND*
5. Clinical documentation and/or support laboratory work are submitted to the validate the applicable criteria, including but not limited to at least ONE (1) of the following:
    a. Fasting lipid panel from within past 3 months; *and/or*
    b. Current statin therapy documentation including dose/duration or statin intolerance; *and/or*
    c. For statin intolerance, specific symptoms and lab evidence (e.g., CK levels); *and/or*
    d. Concurrent lipid-lowering therapies*; and/or*
    e. Other acceptable documentation; *AND*
6. The requested product will be prescribed within the manufacturer's published dosing guidelines or falls within dosing guidelines found in a compendia of current literature*; AND*
7. The member meets the applicable Medical Necessity Criteria for Initial Clinical Review or Subsequent Clinical Review listed below.

Medical Necessity Criteria for Initial Clinical Review

Initial Indication-Specific Criteria

Established Atherosclerotic Cardiovascular Disease (ASCVD)

The Plan considers Praluent (alirocumab) or Repatha (evolocumab) medically necessary when ALL the following are met:

8. The member has clinical documentation showing a history of established ASCVD, defined as ONE (1) or more of the following:
    a. History of acute coronary syndrome/myocardial infarction; *or*
    b. Stable or unstable angina; *or*
    c. Coronary or other arterial revascularization; *or*
    d. Stroke or transient ischemic attack; *or*
    e. Peripheral arterial disease; *or*
    f. Other documented atherosclerotic disease (coronary/carotid/peripheral); *AND*
9. The member meets ONE (1) of the following[s]:
    a. Current LDL-C level ≥55 mg/dL after a minimum three-month trial with at least TWO (2) high-intensity statins (totaling 6 months) used in combination with ezetimibe; *or*
    b. Current LDL-C level ≥55 mg/dL and the member has a documented contraindication or intolerance to statins.

Reducing the Risk of Cardiovascular Events

The Plan considers Praluent (alirocumab) or Repatha (evolocumab) medically necessary when ALL the following are met:

8. The member is at high risk for a major cardiovascular event (see Appendix C, Table 2)*; AND*
9. The member has one ONE (1) of the following (see Appendix C, Table 3):
    a. Atherosclerotic cerebrovascular disease*; or*
    b. Coronary artery disease*; or*
    c. Peripheral arterial disease*; or*
    d. High-risk diabetes mellitus*; AND*
10. The member meets ALL of the following:
    a. No evidence of a history of myocardial infarction*; and*
    b. No evidence of a history of stroke*; AND*
11. The requested drug is being used for primary prevention of cardiovascular events*; AND*
12. The member meets ONE (1) of the following[s]:
    a. Current LDL-C level ≥55 mg/dL after a minimum three-month trial with at least TWO (2) high-intensity statins (totaling 6 months) used in combination with ezetimibe; *or*
    b. Current LDL-C level ≥55 mg/dL and the member has a documented contraindication or intolerance to statins.

If the above prior authorization criteria are met, a Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitor will be approved for up to 6-months.[s]

Treatment of primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH)

The Plan considers Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors medically necessary when ALL the following are met:

8. The member has had an LDL-C level ≥ 190 mg/dL before any lipid-lowering therapies; *AND*
9. The member meets ONE (1) of the following[s]:
    a. Current LDL-C level ≥ 100 mg/dL after a minimum three-month trial with at least TWO (2) high-intensity statins (totaling 6 months) and meets ONE (1) of the following:
        i. Used in combination with ezetimibe; *or*
        ii. Has a documented contraindication or intolerance to ezetimibe; or
    b. Current LDL-C level ≥ 100 mg/dL and the member has a documented contraindication or intolerance to statins.

If the above prior authorization criteria are met, a Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitor will be approved for up to 6-months.[s]

Treatment of homozygous familial hypercholesterolemia (HoFH)

The Plan considers Praluent (alirocumab) or Repatha (evolocumab) medically necessary when ALL the following are met:

8. The member has a diagnosis of HoFH confirmed by ONE (1) of the following:
    a. Genetic testing demonstrating a mutation at the LDL receptor, ApoB, PCSK9, or ARH adaptor protein gene; *or*
    b. Untreated LDL-C higher than 500mg/dL or treated LDL-C ≥300 mg/dL and ONE (1) of the following:
        i. Presence of cutaneous or tendinous xanthoma before the age of 10 years; *or*
        ii. Elevated LDL-C levels consistent with heterozygous familial hypercholesterolemia in both parents; *AND*
9. The member meets ONE (1) of the following[s]:
    a. Current LDL-C level ≥ 100 mg/dL after a minimum three-month trial with at least TWO (2) high-intensity statins (totaling 6 months) and meets ONE (1) of the following:
        i. Used in combination with ezetimibe; *or*
        ii. Has a documented contraindication or intolerance to ezetimibe; *or*
    b. Current LDL-C level ≥ 100 mg/dL and the member has a documented contraindication or intolerance to statins.

If the above prior authorization criteria are met, a Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitor will be approved for up to 6-months.[s]

Continued Care

Medical Necessity Criteria for Subsequent Clinical Review

Subsequent Medical Necessity Criteria

The Plan considers Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors medically necessary when ALL the following are met:

1. The member has chart documentation demonstrating ONE (1) of the following:
    a. A reduction in LDL-C since starting therapy*; or*
    b. Achievement and maintenance of LDL-C goal*; AND*
2. The member will continue to receive maximally tolerated statin therapy, unless contraindicated or not tolerated*; AND*
3. The member is not receiving concurrent therapy with another PCSK9 inhibitor*; AND*
4. The requested product will be prescribed within the manufacturer's published dosing guidelines or falls within dosing guidelines found in a compendia of current literature

If the above reauthorization criteria are met, the requested product will be authorized for up to 12 months.[s]

Experimental or Investigational / Not Medically Necessary[s]

PCSK9 Inhibitors for any other indication is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven.

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Appendix A

Table 1: PCSK9 Inhibitors

Preferred	Non-preferred
Praluent (alirocumab)	Leqvio (inclisiran) Repatha (evolocumab)

NOTE: Prior Authorization is required for all listed products.

Appendix B

The treatment of dyslipidemia involves multiple considerations, as recommended by several prominent professional organizations, including the American College of Cardiology, the American Heart Association, and the American Association of Clinical Endocrinology.

1. Treatment Goals
    - Reduction of elevated atherogenic cholesterol to prevent cardiovascular events

- Reduction of elevated triglyceride levels to prevent acute pancreatitis
- Administration of statin therapy to patients with known cardiovascular disease regardless of baseline LDL-C levels
- Risk assessment for primary prevention of cardiovascular disease in high-risk patients

2. Treatment Targets
    - The intensity of statin therapy for desired reduction of LDL-C levels is set by the American College of Cardiology/American Heart Association guidelines.
    - LDL-C and non-HDL-C levels are set by the American Association of Clinical Endocrinology guideline and National Lipid Association guideline.
3. Treatment Options
    - Lifestyle changes
    - Pharmacologic therapy based on LDL-C levels and risk assessment
4. Recommendations for Specialist Referral
    - Patients with suspected primary or familial forms of dyslipidemia
    - Pregnant patients
    - Patients with diagnosed homozygous or severe heterozygous familial hypercholesterolemia
    - Patients with severe hypertriglyceridemia

These guidelines provide a framework for the management of dyslipidemia, with the ultimate goal of reducing the risk of atherosclerotic cardiovascular disease and associated events. The following tables summarize key recommendations from these diverse guidelines, highlighting the importance of individualized patient care based on specific clinical conditions, tolerability, and potential drug-drug interactions. Regular follow-ups are essential to ensure adherence to therapy and to assess response and side effects.

Summary of Recommendations

Treatment Goals	Specific Recommendations
Reduce atherogenic cholesterol	Use high-intensity statin therapy to reduce LDL-C levels by 50% or more
Reduce triglyceride levels	Depending on severity, recommend lifestyle changes, fibrates, omega-3 fatty acids, or nicotinic acid
Secondary prevention in patients with known CVD	Use high-intensity or maximally tolerated statin therapy
Primary prevention	Statin therapy for patients aged 40-75 years with ≥7.5% 10-year ASCVD risk; lifestyle modifications for all adults

Treatment Intensity	LDL-C Reduction
High Intensity	Reduce LDL-C by 50% or more
Moderate Intensity	Reduce LDL-C by 30%-49%
Low Intensity	Reduce LDL-C by less than 30%

AACE Risk Category	LDL-C (mg/dL)	Non-HDL-C (mg/dL)
Extreme Risk	<55	<80
Very High Risk	<70	<100
High Risk	<100	<130
Moderate Risk	<100	<130
Low Risk	<130	<160

Treatment Options	Specific Recommendations
Lifestyle Changes	Attain and maintain a healthy BMI, healthy diet, physical exercise, cessation of tobacco and alcohol use
Pharmacologic Therapy	Based on LDL-C levels and risk assessment, consider statins, PCSK9 inhibitors, ezetimibe, and monoclonal antibodies

Recommendation for Specialist Referral	Specific Cases
Primary or familial forms of dyslipidemia	LDL-C level ≥190 mg/dL
Pregnancy	Consider non-statin therapies
Diagnosed familial hypercholesterolemia	Treatment intensification as needed
Severe hypertriglyceridemia	Specialist treatment as needed

Appendix C

Table 2: High Risk for Major Cardiovascular Events

Polyvascular disease, defined as coronary, carotid, or peripheral artery stenosis ≥50% at a second location of vascular disease
Diabetes mellitus or metabolic syndrome in a patient with coronary, carotid, or peripheral artery disease

Most recent LDL > 130 mg/dL (> 3.4 mmol/L) or non-HDL > 160 mg/dL (> 4.2 mmol/L)
High sensitive c-reactive protein > 3.0 mg/dL
Current smoker
Men > 65 years of age, women > 70 years of age
2 or more coronary revascularizations (percutaneous or surgical) at least 6 months apart (the most recent CABG may not be within the past 1 year)
2 or more carotid revascularizations (percutaneous or surgical) at least 6 months apart
eGFR < 45 mL/min/1.73 m^2

Table 3: High Cardiovascular Risk Factors - Vascular Disease Evidence

Diagnosis of vascular disease	Evidence supporting diagnosis
Coronary artery disease (at least 1 of the following) without a prior MI:	● Documented coronary artery disease in ≥2 major territories (right, left anterior descending, circumflex) of at least 50% or involving the left main coronary artery of at least 30% diagnosed by invasive or non-invasive coronary imaging ● PCI or CABG > 1 year ago with residual or new disease defined as ≥50% stenosis in a non-revascularized major epicardial vessel with invasive or non-invasive imaging ● Coronary artery calcium score ≥100
Cerebrovascular disease (at least 1 of the following) without a prior stroke:	● Prior transient ischemic attack not due to cardioembolism with ≥50% stenosis in either carotid ● Atheromatous plaque in 2 or more segments of the carotid arteries of ≥50% ● Prior carotid revascularization
Peripheral arterial disease without claudication:	● Invasive or non-invasive imaging evidence of atherosclerosis in any arterial segment in the periphery (excludes vessels in the head, neck, and coronaries) of ≥50% and at least one of the following: ○ Second peripheral artery with > 50% stenosis ○ Atheroma of the thoracic or abdominal aorta ○ ABI < 0.90
Diabetes mellitus with 1 of the following:	● Diabetic nephropathy with either microalbuminuria or estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 ● Stage IV retinopathy ● > 50 years of age and current treatment with insulin ● > 50 years of age and diagnosis ≥10 years ago

ABI, ankle brachial index; CABG, coronary artery bypass grafting; *PCI, percutaneous coronary intervention.*

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