Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors

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

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Atherosclerotic cardiovascular disease (ASCVD) is a broad term that encompasses conditions such as heart attacks, strokes, and angina (chest pain), all resulting from the hardening and narrowing of arteries due to cholesterol accumulation. Similarly, heterozygous familial hypercholesterolemia (HeFH) and homozygous familial hypercholesterolemia (HoFH) are inherited genetic disorders characterized by significantly elevated low-density lipoprotein (LDL) cholesterol levels, with HoFH presenting more severe LDL elevation than HeFH.

Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) inhibitors, including Praluent (alirocumab) and Repatha (evolocumab), have received FDA approval for use in conjunction with dietary changes and statin therapy to reduce LDL cholesterol levels in conditions involving high cholesterol and heart disease. They function by binding to PCSK9, thereby enhancing the quantity of low-density lipoprotein receptors (LDLR), crucial for eliminating LDL cholesterol from the bloodstream. Praluent and Repatha are indicated

for the treatment of HeFH, ASCVD, and HoFH. Leqvio (inclisiran) has been approved for the treatment of HeFH and ASCVD.

While Praluent and Repatha, both approved in 2015, operate in similar ways, Leqvio (inclisiran) is the first FDA-approved drug employing small interfering ribonucleic acid (siRNA) for the treatment of HeFH and ASCVD. Despite the fact that all three medications are administered via subcutaneous (under the skin) injection, Leqvio should only be given by a healthcare professional.

For the latest guidelines, the ACC/AHA recommendations should be reviewed, accessible via the ACC website at https://www.acc.org/guidelines. Other sources of guidelines include the American Association of Clinical Endocrinology and the National Institute for Health and Care Excellence, which may differ in some recommendations.

Table 1: PCSK9 Inhibitors

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

NOTE: Prior Authorization is required for all listed products.

Definitions

"**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.

"**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.

"**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.

"**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.

"**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.

"**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.

Clinical Indications

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

1. The member meets **ALL** the criteria relevant to the product and indications listed below***; AND***
2. Chart documentation and supporting lab work are submitted to validate the applicable criteria***; AND***
3. 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.

Medical Necessity Criteria for Initial Authorization

Praluent (alirocumab)

The Plan considers **Praluent (alirocumab)** medically necessary when **ALL** the following criteria are met for the applicable indication listed below:

Treatment of established atherosclerotic cardiovascular disease (ASCVD)

1. The member has clinical documentation showing a history of established ASCVD**; *AND***
2. The member meets **ONE** of the following:
    a. Current LDL-C level ≥ 70 mg/dL after a minimum three-month trial with at least **TWO** high-intensity statins (totaling 6 months) used in combination with ezetimibe**; *or***
    b. Current LDL-C level ≥ 70 mg/dL and the member has a documented contraindication or intolerance to statins.

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

1. The member has had an LDL-C level ≥ 190 mg/dL before any lipid-lowering therapies**; *AND***
2. The member meets **ONE** of the following:
    a. Current LDL-C level ≥ 100 mg/dL after a minimum three-month trial with at least **TWO** high-intensity statins (totaling 6 months) used in combination with ezetimibe**; *or***

b. Current LDL-C level ≥ 100 mg/dL and the member has a documented contraindication or intolerance to statins.

Treatment of homozygous familial hypercholesterolemia (HoFH)

1. The member has a diagnosis of HoFH confirmed by **ONE** 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** 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***
2. The member has experienced an LDL-C level ≥ 190 mg/dL before any lipid-lowering therapies**; *AND***
3. The member meets **ONE** of the following:
    a. Current LDL-C level ≥ 100 mg/dL after a minimum three-month trial with at least **TWO** high-intensity statins (totaling 6 months) used in combination with 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, Praluent (alirocumab) will be approved for 6 months.

Repatha (evolocumab)

The Plan considers **Repatha (evolocumab)** medically necessary when **ALL** the following criteria are met for the applicable indication listed below:

Treatment of clinical atherosclerotic cardiovascular disease (ASCVD)

1. The member has clinical documentation showing a history of established ASCVD**; *AND***
2. The member meets **ONE** of the following:
    a. Current LDL-C level ≥ 70 mg/dL after a minimum three-month trial with at least **TWO** high-intensity statins (totaling 6 months) used in combination with ezetimibe**; *or***
    b. Current LDL-C level ≥ 70 mg/dL and the member has a documented contraindication or intolerance to statins**; *AND***

3. The member has a documented trial and failure, intolerance to, or contraindication from trying Praluent (alirocumab).

<u>Treatment of primary hyperlipidemia including heterozygous familial hypercholesterolemia (HeFH)</u>

1. The member is 10 years of age or older**; *AND***
2. The member has had an LDL-C level ≥ 190 mg/dL before any lipid-lowering therapies**; *AND***
3. The member meets **ONE** of the following:
    a. Current LDL-C level ≥ 100 mg/dL after a minimum three-month trial with at least **TWO** high-intensity statins (totaling 6 months) used in combination with ezetimibe**; *or***
    b. Current LDL-C level ≥ 100 mg/dL and the member has a documented contraindication or intolerance to statins**; *AND***
4. The member has a documented trial and failure, intolerance to, or contraindication to trying Praluent (alirocumab).

<u>Treatment of homozygous familial hypercholesterolemia (HoFH)</u>

1. The member is 10 years of age or older**; *AND***
2. The member has a diagnosis of HoFH confirmed by **ONE** 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** 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***
3. The member has experienced an LDL-C level ≥ 190 mg/dL before any lipid-lowering therapies**; *AND***
4. The member meets **ONE** of the following:
    a. Current LDL-C level ≥ 100 mg/dL after a minimum three-month trial with at least **TWO** high-intensity statins (totaling 6 months) used in combination with ezetimibe**; *or***
    b. Current LDL-C level ≥ 100 mg/dL and the member has a documented contraindication or intolerance to statins**; *AND***
5. The member has a documented trial and failure, intolerance to, or contraindication to trying Praluent (alirocumab).

If the above prior authorization criteria are met, Repatha (evolocumab) will be approved for 6 months.

Leqvio (inclisiran)

The Plan considers **Leqvio (inclisiran)** medically necessary when **ALL** the following criteria are met for the applicable indication listed below:

For the treatment of clinical atherosclerotic cardiovascular disease (ASCVD)

1. The member has clinical documentation showing a history of established ASCVD**; *AND***
2. The member meets **ONE** of the following:
    a. Current LDL-C level ≥ 70 mg/dL after a minimum three-month trial with at least **TWO** high-intensity statins (totaling 6 months) used in combination with ezetimibe***; or***
    b. Current LDL-C level ≥ 70 mg/dL and the member has a documented contraindication or intolerance to statins**; *AND***
3. The member has a documented trial and failure, intolerance to, or contraindication from trying Praluent (alirocumab).

For the treatment of heterozygous familial hypercholesterolemia (HeFH)

1. The member has experienced LDL-C level ≥ 190 mg/dL prior to any lipid-lowering therapies**; *AND***
2. The member meets **ONE** of the following:
    a. Current LDL-C level ≥ 100 mg/dL after a minimum three-month trial with at least **TWO** high-intensity statins (totaling 6 months) used in combination with ezetimibe***; or***
    b. Current LDL-C level ≥ 100 mg/dL and the member has a documented contraindication or intolerance to statins**; *AND***
3. The member has a documented trial and failure, intolerance to, or contraindication to trying Praluent (alirocumab).

If the above prior authorization criteria are met, Leqvio (inclisiran) will be approved for 6 months.

Medical Necessity Criteria for Reauthorization

Reauthorization of 12 months will be granted if the member has chart documentation demonstrating a clinical improvement in symptoms since starting the requested medication and **ONE** of the following criteria is met:

1. The member has shown a reduction in LDL-C since starting the requested medication**; *OR***
2. The member has reached the LDL-C goal and has maintained LDL-C levels

Experimental or Investigational / Not Medically Necessary

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

Appendix

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

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