Clinical Guideline

Oscar Clinical Guideline: Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors (PG068, Ver. 6)

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

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 patients with certain conditions, including, as adjunct therapy for:

1. Atherosclerotic cardiovascular disease (ASCVD), to reduce risk of myocardial infarction, stroke, and coronary revascularization in adults with established ASCVD.
2. Heterozygous familial hypercholesterolemia (HeFH).
3. Homozygous familial hypercholesterolemia (HoFH).

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 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.

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.

Medical Necessity Criteria for Initial Authorization

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

1. 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***
2. 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)***; AND***
3. Will not be used concomitantly with other PCSK9 inhibitors (i.e., must discontinue current therapy before initiating different agent)***; AND***
4. Clinical documentation and/or support laboratory work are submitted to the validate the applicable criteria, including but not limited to:
    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***
5. 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***
6. The member meets **ALL** the criteria relevant to the applicable indication listed below:

Treatment of established atherosclerotic cardiovascular disease (ASCVD)

7. The member has clinical documentation showing a history of established ASCVD, defined as **ONE** 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***

8. 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)

7. The member has had an LDL-C level ≥ 190 mg/dL before any lipid-lowering therapies**; *AND***
8. 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); (Praluent and Repatha only)

7. 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***
8. 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.

Medical Necessity Criteria for Reauthorization

Reauthorization for 12 months will be granted if **BOTH** of the following criteria are met:

1. The member has chart documentation demonstrating **ONE** 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

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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