



Drug and Biologic Coverage Policy

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Coverage Policy Number 1509

PCSK9 Inhibitors

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Related Coverage Resources

[Genetic Testing of Heritable Disorders](#)

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INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

PCSK9 Inhibitors include:

- **Praluent®** (alirocumab)
- **Repatha®** (evolocumab)

Repatha (evolocumab)

Evolocumab (Repatha) is considered medically necessary for the treatment of hyperlipidemia in an adult (18 years or older) when ALL of the following criteria are met:

- **Individual has documentation of EITHER of the following:**
 - **Established clinical atherosclerotic cardiovascular disease (ASCVD) as evidenced by any of the following:**
 - Coronary heart disease (acute coronary syndromes, history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization)
 - Cerebrovascular disease (stroke, transient ischemic attack)
 - Peripheral arterial disease (PAD) of atherosclerotic origin
 - **Primary Hyperlipidemia (Including Heterozygous Familial Hypercholesterolemia) as defined by one of the following:**

- WHO Criteria (Dutch Lipid Network clinical criteria, score greater than 5; see [Appendix 1](#))
 - Simon-Broome Criteria (threshold met for “definite” or “possible” familial hypercholesterolemia, see [Appendix 2](#))
 - Confirmed genetic testing
 - LDL-C \geq 190 mg/dL (prior to treatment with antihyperlipidemic agents)
 - Clinical manifestations of HeFH (e.g., cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma)
- **ONE of the following:**
 - Documented contraindication per FDA label to statin therapy
 - Documented intolerance to at least TWO statins with symptoms or abnormal lab results being temporally related to statin and other causes being ruled out
 - Inadequate response (LDL-C greater than 70 mg/dL) when ALL of the following criteria are met:
 - Lipid lowering therapy with statins defined as **EITHER** of the following:
 - **High-intensity statin therapy** (atorvastatin 40-80 mg/day or rosuvastatin 20-40 mg/day)
 - **Moderate intensity, or low intensity statin therapy** and documented intolerance to atorvastatin 40-80 mg/day or rosuvastatin 20-40 mg/day
 - Statin therapy is used in combination with ezetimibe (Zetia) OR there is a contraindication per FDA label, documented intolerance, or the individual is not a candidate for ezetimibe (for example, LDL-C lowering to achieve target exceeds 15-20%)
 - Regimen has been taken for a minimum duration of 12 consecutive weeks
 - **Use is adjunctive to diet and maximally tolerated statin therapy (unless contraindicated or intolerant)**

Evolocumab (Repatha) is considered medically necessary for the treatment of homozygous familial hypercholesterolemia (HoFH) in an individual 13 years of age or older when ALL of the following criteria are met:

- **Documented diagnosis of HoFH as demonstrated by EITHER of the following:**
 - Genetic confirmation of 2 mutant alleles at the LDL receptor, ApoB, PCSK9 or ARH adaptor protein gene locus
 - An untreated LDL-C greater than 500 mg/dL OR a total treated LDL-C greater than or equal to 300 mg/dL AND one of the following:
 - Cutaneous or tendinous xanthoma before the age of 10 years
 - Untreated LDL-C levels consistent with heterozygous familial hypercholesterolemia in both parents (greater than 190 mg/dL)
- **Inadequate response (LDL-C greater than 70 mg/dL) with maximally tolerated lipid lowering therapy regimen (for example, high-intensity statin, ezetimibe, LDL apheresis) AND use will be adjunctive to diet and maximally tolerated lipid lowering therapy (unless contraindicated or intolerant)**
- **Will not be used in combination with lomitapide (Juxtapid®)**

Praluent (alirocumab)

Alirocumab (Praluent) is considered medically necessary for the treatment of hyperlipidemia in an adult (18 years or older) when ALL of the following criteria are met:

- **Criteria listed above for evolocumab (Repatha) for the treatment of hyperlipidemia are met**
- **Either of the following:**
 - Not a candidate for evolocumab (Repatha) prefilled syringe or autoinjector due to documented latex sensitivity AND inability to use the Repatha on-body infusor
 - Documented intolerance to evolocumab (Repatha)

Initial authorization of alirocumab (Praluent) or evolocumab (Repatha) is up to 6 months

- For Repatha, the dose approved for ASCVD/HeFH is 140 mg every 2 weeks OR 420 mg monthly via Repatha Pushtronex
- The dose of Repatha approved for HoFH is 420 mg once monthly.
- For Praluent, the recommended starting dose of Praluent is 75 mg once every 2 weeks. An alternative starting dosage is 300 mg once every 4 weeks. For patients receiving Praluent 75 mg every 2 weeks, the dosage may be adjusted to the maximum dosage of 150 mg administered every 2 weeks. For patients receiving Praluent 300 mg every 4 weeks, the dosage may be adjusted to 150 mg every 2 weeks starting the new dose on the next scheduled dosing date.
- The recommended dose of Praluent in patients with HeFH undergoing LDL apheresis is 150 mg once every 2 weeks.

Alirocumab (Praluent) or evolocumab (Repatha) are considered medically necessary for continued use when BOTH of the following are met:

- Initial criteria listed above are met
- Documented evidence of clinical beneficial response (for example, demonstrated reduction of LDL-C)

Reauthorization is up to 12 months

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

The use of PCSK9 Inhibitors are considered experimental, investigational or unproven for ANY other use including the following:

- Concurrent use of either alirocumab (Praluent) or evolocumab (Repatha) with each other or in combination with lomitapide (Juxtapid)
- Use of PCSK9 inhibitors for individuals with 2 null LDLR pathogenic variants and/or LDL receptor activity less than 2%

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

FDA Approved Indications

Drug	FDA Approved Indications
Praluent (alirocumab)	Prevention of Cardiovascular Events Praluent is indicated to reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease. Primary Hyperlipidemia (Including Heterozygous Familial Hypercholesterolemia) Praluent is indicated 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 to reduce low-density lipoprotein cholesterol (LDL-C).
Repatha (evolocumab)	Prevention of Cardiovascular Events In adults with established cardiovascular disease, Repatha is indicated to reduce the risk of myocardial infarction, stroke, and coronary revascularization. Primary Hyperlipidemia (Including Heterozygous Familial Hypercholesterolemia) Repatha is indicated 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 to reduce low-density lipoprotein cholesterol (LDL-C).

Drug	FDA Approved Indications
	<p>Homozygous Familial Hypercholesterolemia</p> <p>Repatha is indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) for the treatment of patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.</p>

Recommended Dosing

Drug	FDA Recommended Dosing
<p>Praluent (alirocumab)</p>	<p>The recommended starting dose of Praluent is 75 mg once every 2 weeks administered subcutaneously, since the majority of patients achieve sufficient LDL-C reduction with this dosage. An alternative starting dosage for patients who prefer less frequent dosing is 300 mg once every 4 weeks (monthly).</p> <p>For patients receiving Praluent 75 mg every 2 weeks, measure LDL-C levels within 4 to 8 weeks of initiating Praluent. If the LDL-C response is inadequate, the dosage may be adjusted to the maximum dosage of 150 mg administered every 2 weeks. Reassess LDL-C within 4 to 8 weeks.</p> <p>For patients receiving Praluent 300 mg every 4 weeks, measure LDL-C just prior to the next scheduled dose, since in some patients LDL-C can vary considerably between doses with this regimen. If LDL-C reduction is inadequate, the dosage may be adjusted to 150 mg every 2 weeks, starting the new dose on the next scheduled dosing date. Reassess LDL-C within 4 to 8 weeks.</p> <p>If an every-2-week dose is missed, instruct the patient to administer the injection within 7 days from the missed dose and then resume the patient's original schedule. If the missed dose is not administered within 7 days, instruct the patient to wait until the next dose on the original schedule.</p> <p>If an every-4-week dose is missed, instruct the patient to administer the injection within 7 days from the missed dose and then resume the patient's original schedule. If the missed dose is not administered within 7 days, instruct the patient to administer the dose, starting a new schedule based on this date.</p> <p>The recommended dose of Praluent in patients with HeFH undergoing LDL apheresis is 150 mg once every 2 weeks. Praluent can be administered without regard to the timing of apheresis.</p>
<p>Repatha (evolocumab)</p>	<p>The recommended subcutaneous dosage of Repatha in adults with established cardiovascular disease or in adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH]) is either 140 mg every 2 weeks OR 420 mg once monthly, based on patient preference for dosing frequency and injection volume. When switching dosage regimens, administer the first dose of the new regimen on the next scheduled date of the prior regimen.</p> <p>The recommended subcutaneous dosage of Repatha in patients with HoFH is 420 mg once monthly. In patients with HoFH, measure LDL-C levels 4 to 8 weeks after starting Repatha, since response to therapy will depend on the degree of LDL-receptor function.</p>

Drug	FDA Recommended Dosing
	<p>When monitoring LDL-C for patients receiving Repatha 420 mg once monthly, note that LDL-C can vary considerably during the dosing interval in some patients [see <i>Clinical Studies</i>].</p> <p>If a dose is missed, instruct the patient to administer Repatha within 7 days from the missed dose and resume the patient's original schedule.</p> <ul style="list-style-type: none"> ▪ If an every-2-week dose is not administered within 7 days, instruct the patient to wait until the next dose on the original schedule. ▪ If a once-monthly dose is not administered within 7 days, instruct the patient to administer the dose and start a new schedule based on this date.

Drug Availability

Drug	Drug Availability
Praluent (alirocumab)	Available for injection as single-dose pre-filled pens or syringes as 75 mg/mL or 150 mg/mL in packages of 1 pen or syringe or 2 pens or syringes.
Repatha (evolocumab)	<p>Available for injection as a 140 mg/mL solution in a single-use prefilled syringe or SureClick® autoinjector in packages of 1 syringe or 1, 2, or 3 SureClick® autoinjectors. Also available as 420 mg/3.5 mL solution in a single-use Pushtronex™ system (on-body infusor with prefilled cartridge).</p> <p>Advise latex-sensitive patients that the following components contain dry natural rubber (a derivative of latex) that may cause allergic reactions in individuals sensitive to latex: the needle cover of the glass single-use prefilled syringe and the single-use prefilled autoinjector.</p> <p>The single-use on-body infusor with prefilled cartridge is NOT made with natural rubber latex.</p>

General Background

OVERVIEW

Praluent (alirocumab) is indicated for the following uses:¹

- Established cardiovascular (CV) disease, in adults to reduce the risk of myocardial infarction (MI), stroke, and unstable angina requiring hospitalization.
- Primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH]), in adults as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe) to reduce low-density lipoprotein cholesterol (LDL-C).

The safety and efficacy of Praluent in children have not been established.¹

Repatha (evolocumab) is indicated for the following uses:²

- Established cardiovascular (CV) disease, in adults to reduce the risk of myocardial infarction (MI), stroke, and coronary revascularization.
- Primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH]), in adults as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe) to reduce low-density lipoprotein cholesterol (LDL-C).
- Homozygous familial hypercholesterolemia (HoFH), as an adjunct to diet and other low-density lipoprotein (LDL)-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients who require additional lowering of LDL-C.

The safety and effectiveness of Repatha have not been established in pediatric patients with primary hyperlipidemia or HeFH. The safety and effectiveness of Repatha have not been established in pediatric patients with HoFH aged < 13 years.¹

Guidelines

Many guidelines are available regarding the treatment of patients with dyslipidemia.³⁻¹⁰ For patients with elevated LDL-C, statins are the cornerstone of therapy and recommended first-line to be used at maximally tolerated doses due to the established benefits regarding the reduction of CV risks. Atorvastatin 40 mg to 80 mg once daily (QD) and rosuvastatin 20 mg to 40 mg QD are considered high-intensity statins as they achieve LDL-C lowering of $\geq 50\%$. The American Heart Association/American College of Cardiology guidelines on the management of blood cholesterol (2018) defines atherosclerotic cardiovascular disease (ASCVD) as an acute coronary syndrome (ACS), those with a history of MI, stable or unstable angina or coronary or other revascularizations, stroke, transient ischemic attack (TIA), or peripheral arterial disease (PAD).¹⁰ Although LDL-C thresholds are not always recognized, in general, an LDL-C < 70 mg/dL is recommended for most patients with ASCVD to reduce CV risk. Use of a PCSK9 as an adjunct is justified if this goal is not met with maximally tolerated statins.¹⁰ Additionally, guidelines and reviews have recognized that patients with a coronary artery calcium or calcification score ≥ 300 Agatston units are at an increased risk of CV events.¹⁰⁻¹³

The National Lipid Association (NLA) published guidelines for the screening, diagnosis, and management of pediatric and adult patients with familial hypercholesterolemia (2011).¹⁴ Familial hypercholesterolemia encompasses a group of genetic defects that cause severe elevations in LDL-C levels, as well as other lipid parameters. HeFH occurs in approximately 1 in 300 to 500 patients and is present in childhood. Total cholesterol (total-C) levels in HeFH range from 350 to 550 mg/dL, which can result in premature ASCVD. Aggressive lipid-lowering therapy is recommended to achieve LDL-C reductions of at least 50%. Both children and adults with LDL-C levels ≥ 190 mg/dL following lifestyle modifications will require medication therapy. Statins are the initial treatment for all adults with familial hypercholesterolemia. High or moderate intensity statins are recommended; low potency statins are generally inadequate for patients with familial hypercholesterolemia due to the markedly elevated LDL-C levels. In the pivotal trials for Praluent, HeFH was diagnosed utilizing Simon Broome criteria or Dutch Lipid Clinical Network criteria.¹

In an AHA scientific statement, it describes the Dutch Lipid Clinical Network Criteria and states that a score of > 5 on the scale makes the diagnosis of familial hypercholesterolemia highly probable.¹⁵ Also, genetic testing can reveal a diagnosis of HeFH and clinical manifestations (e.g., tendon xanthomata) are highly suggestive of the condition. Also, patients with an untreated LDL-C ≥ 190 mg/dL suggest familial hypercholesterolemia.¹⁵⁻¹⁷ In general, for patients with HeFH who have not yet manifested ASCVD, LDL-C levels ≤ 100 mg/dL are recommended. The addition of a PCSK9 inhibitor to statin therapy can be considered if this goal is not achieved. In 2019 the AHA issued a scientific statement regarding statin safety and associated adverse events.¹⁸

In general, statins are well-tolerated agents that have successfully led to decreased LDL-C levels which reduce CV events (e.g., MI, ischemic stroke). The risk of serious statin-induced muscle injury (e.g., rhabdomyolysis) is low (< 0.01%). In US clinical practice, about 10% of patients stop taking statin therapy due to subjective complaints, of which muscle symptoms without significantly raised creatine kinase levels are noted. Data suggests that the muscle symptoms that occur among patients are not caused by the pharmacologic effects of the statin and restarting statin therapy for these patients is important, especially among patients at high risk of CV events, for whom CV event prevention is important. Several studies have shown that patients believed that they were “statin intolerant”. However, many patients were able to subsequently tolerate a statin upon rechallenge and receive the benefits provided with these agents. Other data support this occurrence.^{19,20} The 2014 HoFH position paper from the Consensus Panel on familial hypercholesterolemia of the European Atherosclerosis Society states the diagnosis of HoFH is made based on genetic or clinical criteria.¹⁷ A definitive diagnosis can be made by genetic confirmation of two mutant alleles at the low density lipoprotein receptor, apolipoprotein B, PCSK9, or low-density lipoprotein receptor adaptor protein 1 gene locus. However, in some patients genetic confirmation remains elusive. Historically, HoFH has been commonly diagnosed based on LDL-C levels such as an untreated LDL-C > 500 mg/dL, or a treated LDL-C ≥ 300 mg/dL. Also confirming the diagnosis is the presence of xanthomas (cutaneous or tendinous) before the age of 10 years or a family history of elevated LDL-C levels consistent with HeFH in both parents.¹⁷ Other clinical manifestations of HoFH include arcus cornea or xanthelasma.^{14,17}

Experimental, Investigational, Unproven Uses

- Concurrent use of evolocumab (Repatha) with alirocumab (Praluent) or lomitapide (Juxtapid). Praluent and Repatha are both PCSK9 inhibitor and should not be used concurrently.^{1,2} Juxtapid, a microsomal triglyceride transfer protein inhibitor, is indicated as an adjunct to lipid-lowering medications and diet to modify lipid parameters (e.g., reduce LDL-C levels) in patients with HoFH.²¹ The efficacy and safety of using Praluent or Juxtapid in combination with Repatha have not been established.
- PCSK9 inhibitors work by preventing PCSK9 from binding to the LDLR receptor, which leads to receptor breakdown. With PCSK9 inhibition, the LDLR receptor can be recycled to the liver for further use to decrease LDL levels. This requires a functional LDL receptor to be effective. Therefore, homozygous or compound heterozygous LDLR genetics null mutations are not recommended for PCSK9 therapy as the medication is not effective without a functional LDLR gene.²²

APPENDIX 1 – WHO Criteria (Dutch Lipid Network Clinical Criteria) for Diagnosis of Heterozygous Familial Hypercholesterolemia (HeFH) (Nordestgaard, 2013)

Diagnostic Scoring for Heterozygous Familial Hypercholesterolemia			
Family History			
First degree relative with known premature (men < 55 yrs, women < 60 yrs) coronary vascular disease			1
First degree relative with known LDL-cholesterol >95 th percentile for age and sex			
and/or			
First degree relative with tendon xanthomata and/or arcus cornealis			2
Children below 18 yrs with LDL-cholesterol >95 th percentile for age and sex			
Clinical History			
Patient has premature (men < 55 yrs, women < 60 yrs) coronary artery disease			2
Patient has premature (men < 55 yrs, women < 60 yrs) cerebral or peripheral vascular disease			1
Physical Examination			
Tendon xanthomata			6
Arcus cornealis below the age of 45 yrs			4
Laboratory Analysis			
	mmol/L	mg/dL	
LDL-cholesterol	> 8.5	> 330	8
LDL-cholesterol	6.5 – 8.4	250 – 329	5
LDL-cholesterol	5.0 – 6.4	190 – 249	3
LDL-cholesterol	4.0 – 4.9	155 – 189	1
(HDL-cholesterol and triglycerides are normal)			
DNA Analysis			
Functional mutation low-density lipoprotein receptor gene present			6
Diagnosis of HeFH is:			
Certain When		> 8 points	
Probable When		6-8 points	
Possible When		3-5 points	

APPENDIX 2 – Simon Broome Register Diagnostic Criteria for Heterozygous Familial Hypercholesterolemia (HeFH) (Scientific Steering Committee, 1991)

Definite familial hypercholesterolemia is defined as:

- Total cholesterol > 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years or total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult. (Levels either pre-treatment or highest on treatment)

PLUS

- Tendon xanthomas in patient or in 1st degree relative (parent, sibling, child), or in 2nd degree relative (grandparent, uncle, aunt)

OR

- DNA-based evidence of an LDL receptor mutation or familial defective apo B-100

Possible familial hypercholesterolemia is defined as:

- Total cholesterol > 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years or total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult. (Levels either pre-treatment or highest on treatment)

And at least one of the following:

- Family history of myocardial infarction below 50 years of age in 2nd degree relative or below 60 years of age in 1st degree relative.
- Family history of raised cholesterol > 7.5 mmol/L (290 mg/dL) in adult 1st or 2nd degree relative or > 6.7 mmol/L (260 mg/dL) in child or sibling under 16 years of age.

Table 1: High-, Moderate-, and Low-Intensity Statin Therapy⁴

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
<u>Daily dose lowers LDL-C, on average, by approximately > 50%</u> Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	<u>Daily dose lowers LDL-C, on average, by approximately 30% to < 50%</u> Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 2-4 mg	<u>Daily dose lowers LDL-C, on average, by < 30%</u> Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg

Coding/ Billing Information

Note: PCSK9 Inhibitors are typically covered under pharmacy benefit plans. Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed. Medical drug coding and diagnosis codes, however, are generally not required for pharmacy claims submissions, therefore, this section is not in use.

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