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Alirocumab

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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.

Overview

This policy supports medical necessity review for alirocumab (**Praluent®**).

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

Medical Necessity Criteria

Alirocumab (Praluent) is considered medically necessary when ONE of the following is met (1, 2, 3, or 4):

1. **Atherosclerotic Cardiovascular Disease.** Individual meets **ALL** of the following criteria (A, B, C, D, E, and F):
    A. Individual is 18 years of age or older
    B. Documentation of **ONE** of the following conditions or diagnoses (i, ii, iii, iv or v):
        i. A previous myocardial infarction or a history of an acute coronary syndrome
        ii. Angina (stable or unstable)
        iii. A past history of stroke or transient ischemic attack

iv. Peripheral arterial disease (PAD) of atherosclerotic origin
v. Individual has undergone a coronary or other arterial revascularization procedure in the past (for example, coronary artery bypass graft surgery, percutaneous coronary intervention, angioplasty, or coronary stent procedures)

C. Individual meets **ONE** of the following criteria (i or ii):
   i. Documented contraindication or intolerance to statin therapy
   ii. Individual meets **BOTH** of the following (a and b):
      a. Documented trial of **ONE** high-intensity statin therapy (for example, atorvastatin 40 mg daily or higher; rosuvastatin 20 mg daily or higher [as a single-entity or as a combination product]) for at least 8 continuous weeks
      b. Low-density lipoprotein cholesterol level after this treatment remains at 70 mg/dL or higher

D. Use is adjunctive to diet and maximally tolerated statin therapy [unless contraindicated or intolerant (Appendix A)]

E. Medication is prescribed by, or in consultation with, a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular (CV) risk management and/or lipid disorders

F. Individual meets the preferred covered alternative(s) criteria as indicated in the table below

2. **Heterozygous Familial Hypercholesterolemia.** Individual meets **ALL** of the following criteria (A, B, C, D, E, and F):

A. Individual is 18 years of age or older

B. Individual meets **ONE** of the following criteria (i, ii, or iii):
   i. Individual has an untreated low-density lipoprotein cholesterol (LDL-C) of at least 190 mg/dL (prior to treatment with any antihyperlipidemic agents)
   ii. Individual has genetic confirmation of HeFH by mutations in the low-density lipoprotein receptor, apolipoprotein B, proprotein convertase subtilisin kexin type 9, or low-density lipoprotein receptor adaptor protein 1 gene
   iii. Individual has been diagnosed with HeFH meeting **ONE** of the following diagnostic criteria thresholds (a or b):
      a. Individual meets **BOTH** of the following [1) and 2)]:
         1) Prescriber used the Dutch Lipid Network criteria to diagnose HeFH (Appendix C)
         2) Individual had a score greater than 5
      b. Individual meets **BOTH** of the following [1) and 2)]:
         1) Prescriber used the Simon Broome criteria to diagnose heterozygous familial hypercholesterolemia (Appendix B)
         2) Individual met the threshold for “definite” or “possible (or probable)” familial hypercholesterolemia

C. Individual meets **ONE** of the following criteria (i or ii):
   i. Documented contraindication or intolerance to statin therapy
   ii. Individual meets **BOTH** of the following (a and b):
      a. Documented trial of **ONE** high-intensity statin therapy (for example, atorvastatin 40 mg daily or higher; rosuvastatin 20 mg daily or higher [as a single-entity or as a combination product]) for at least 8 continuous weeks
      b. Low-density lipoprotein cholesterol level after this treatment remains at 70 mg/dL or higher

D. Use is adjunctive to diet and maximally tolerated statin therapy [unless contraindicated or intolerant (Appendix A)]

E. Medication is prescribed by, or in consultation with, a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular (CV) risk management and/or lipid disorders

F. Individual meets the preferred covered alternative(s) criteria as indicated in the table below

3. **Homozygous Familial Hypercholesterolemia (HoFH).** Individual meets **ALL** of the following criteria (A, B, C, D, E, and F):

A. Individual is 18 years of age or older
B. Individual meets **ONE** of the following (i, ii, or iii):
    i. Individual has genetic confirmation of two mutant alleles at the low-density lipoprotein receptor, apolipoprotein B, proprotein convertase subtilisin kexin type 9 (PCSK9), or low-density lipoprotein receptor adaptor protein 1 gene locus
    ii. Individual has an untreated low-density lipoprotein (LDL-C) level of at least 500 mg/dL (prior to treatment with any antihyperlipidemic agent) AND meets **ONE** of the following (a or b):
        a. Individual had clinical manifestations of HoFH before 10 years of age (for example, cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas, or xanthelasma)
        b. Both parents of the individual had untreated LDL-C levels or total cholesterol levels consistent with heterozygous familial hypercholesterolemia (HeFH) (for example, both parents had an untreated LDL-C level of at least 190 mg/dL and/or an untreated total cholesterol level greater than 250 mg/dL
    iii. Individual has a treated LDL-C level ≥ 300 mg/dL AND meets **ONE** of the following (a or b):
    Treated refers to after therapy with at least one antihyperlipidemic agent. Some examples of antihyperlipidemic agents include statins (e.g., atorvastatin, rosuvastatin, lovastatin, simvastatin, pravastatin), ezetimibe, a PCSK9 inhibitor (e.g., Praluent [alirocumab injection]), Evkeeza (evinacumab-dgnb injection), or Juxtapid (lomitapide capsules).
        a. Individual had clinical manifestations of HoFH before 10 years of age (for example, cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma)
        b. Both parents of the individual had untreated LDL-C levels or total cholesterol levels consistent with HeFH (for example, both parents had an untreated LDL-C of at least 190 mg/dL and/or an untreated total cholesterol level greater than 250 mg/dL
C. Individual meets **ONE** of the following criteria (i or ii):
    i. Documented contraindication or intolerance to statin therapy
    ii. Individual meets **BOTH** of the following (a and b):
        a. Documented trial of **ONE** high-intensity statin therapy (for example, atorvastatin 40 mg daily or higher; rosuvastatin 20 mg daily or higher [as a single-entity or as a combination product]) for at least 8 continuous weeks
        b. Low-density lipoprotein cholesterol level after this treatment remains at 70 mg/dL or higher
D. Use is adjunctive to diet and maximally tolerated statin therapy [unless contraindicated or intolerant (Appendix A)]
E. Medication is prescribed by, or in consultation with, a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular (CV) risk management and/or lipid disorders
F. Individual meets the preferred covered alternative(s) criteria as indicated in the table below

4. **Primary Hyperlipidemia.** Individual meets **ALL** of the following criteria (A, B, C, D, E, and F):
This is not associated with atherosclerotic cardiovascular disease (ASCVD), heterozygous familial hypercholesterolemia (HeFH), or homozygous familial hypercholesterolemia (HoFH) and may be referred to as combined hyperlipidemia, hypercholesterolemia (pure, primary), dyslipidemia, or increased/elevated low-density lipoprotein cholesterol (LDL-C) levels.

    A. Individual is 18 years of age or older
    B. Individual meets **ONE** of the following (i or ii):
        i. Individual has a coronary artery calcium or calcification score of 100 or greater Agatston units or 75th percentile or greater for the individual's age, gender and ethnicity [coronary calcium scan may require prior authorization].
        ii. Calculated 10 year ASCVD risk score of 7.5% or higher

C. Individual meets **ONE** of the following criteria (i or ii):
    i. Documented contraindication or intolerance to statin therapy
    ii. Individual meets **BOTH** of the following (a and b):
        a. Documented trial of **ONE** high-intensity statin therapy (for example, atorvastatin 40 mg daily or higher; rosuvastatin 20 mg daily or higher [as a single-entity or as a combination product]) for at least 8 continuous weeks
        b. LDL-C level after this treatment regimen remains at 100 mg/dL or higher (for diabetic individuals at 70mg/dL or higher)
D. Use is adjunctive to diet and maximally tolerated statin therapy [unless contraindicated or intolerant (Appendix A)]
E. Medication is prescribed by, or in consultation with, a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular (CV) risk management and/or lipid disorders
F. Individual meets the preferred covered alternative(s) criteria as indicated in the table below

Coverage varies across plans and requires the use of preferred products. Refer to the customer's benefit plan document for coverage details.

Employer Group and Individual and Family Plans Non-Covered Products and the Preferred Covered Alternatives:

Non-Covered Product	Criteria
Praluent® (alirocumab)	There is documentation the individual has had an inadequate response, contraindication or is intolerant to the following: A. **Repatha**® (evolocumab) [may require prior authorization]

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.

Reauthorization Criteria

Alirocumab (Praluent) is considered medically necessary for continued use when initial criteria are met AND there is documentation of beneficial response (for example, demonstrated reduction of LDL-C).

Authorization Duration

Initial approval duration: up to 12 months
Reauthorization approval duration: up to 12 months

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

1. **Concurrent use of Praluent with Repatha (evolocumab subcutaneous injection) or Leqvio (inclisiran subcutaneous injection).** Repatha is another PCSK9 inhibitor and should not be used with Praluent.[2] Leqvio, a small interfering ribonucleic acid (RNA) directed to PCSK9 messenger RNA, is a similar product and should not be given with Praluent.

Background

OVERVIEW
Praluent, a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor antibody, 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).
- **Homozygous familial hypercholesterolemia (HoFH)**, in adults as an adjunct to other LDL-C lowering therapies, to reduce LDL-C.

The safety and efficacy of Praluent in children have not been established.[1] Repatha® (evolocumab subcutaneous injection) is another PCSK9 inhibitor.[2] Leqvio® (inclisiran subcutaneous injection), a small interfering ribonucleic acid (RNA) directed to PCSK9 messenger RNA, is a similar product.[3]

Guidelines
Many guidelines are available regarding the treatment of patients with dyslipidemia.[4-10] 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 ≥ 50%. Ezetimibe is usually the next therapy added.

- The **American College of Cardiology Expert Consensus Decision Pathway on the Role of Non-Statin Therapies** for LDL-Cholesterol Lowering in the Management of Atherosclerotic cardiovascular disease (ASCVD) Risk (2022) make several recommendations regarding PCSK9 inhibitors.[4] For adults with clinical ASCVD at very high risk (e.g., patients with major ASCVD events, HeFH, diabetes) who are on statin therapy for secondary prevention, the general goal is ≥ 50% LDL-C reduction and an LDL-C < 55 mg/dL with maximally tolerated statin therapy. If the above goals are not achieved, the initial non-statin agents recommended include ezetimibe and/or a PCSK9 monoclonal antibody (i.e., Repatha or Praluent). For adults without clinical ASCVD or diabetes or LDL-C ≥ 190 mg/dL who have undergone subclinical atherosclerosis imaging, if the coronary artery calcium score is ≥ 1,000 Agatston units, PCSK9 monoclonal antibodies (i.e., Repatha or Praluent) may be non-statin agents to consider following high-intensity statin therapy and ezetimibe to achieve the goal of a ≥ 50% LDL-C reduction (and LDL-C threshold < 70 mg/dL).
- The **American Heart Association/American College of Cardiology guidelines on the management of blood cholesterol** (updated 2018) defines ASCVD as an acute coronary syndrome, those with a history of MI, stable or unstable angina or coronary or other revascularizations, stroke, transient ischemic attack, or peripheral arterial disease.[5,6] 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.[5,6] Additionally, guidelines and reviews have recognized that patients with an elevated coronary artery calcium or calcification score (e.g., ≥ 300 Agatston units) are at an increased risk of CV events.[8,11-14]
- The **National Lipid Association** published guidelines for the screening, diagnosis, and management of pediatric and adult patients with familial hypercholesterolemia (2011).[9] Genetic testing can identify HoFH and HeFH in some cases. Also, HeFH can be diagnosed utilizing Simon Broome criteria or Dutch Lipid Clinical Network criteria. Patients with an untreated LDL-C ≥ 190 mg/dL suggest familial hypercholesterolemia. Statins are the initial treatment for all adults with familial hypercholesterolemia, usually at high-potency doses. Ezetimibe can also be added. In general, for patients with HeFH who have not yet manifested ASCVD, LDL-C levels ≤ 100 mg/dL are recommended.
- 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.[15] 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. Other clinical manifestations of HoFH include arcus cornea or xanthelasma. Initial therapy for HoFH is high-intensity statins.[15] Other guidelines note that ezetimibe and PCSK9 inhibitors can be added for patients with HoFH if further reductions are needed; Juxtapid® (lomitapide capsules) and Evkeeza® (evinacumab-dgnb intravenous infusion) can be considered.[4]

Appendix A

Statin Intolerance
Statin intolerance occurs when an individual is unable to continue to use a statin, either because of the development of a side effect or because of evidence on a blood test that certain markers of liver function or muscle function (creatine kinase) are sufficiently abnormal to cause concern. The intolerance can be either partial (for example, only some statins at some doses) or complete (for example, all statins at any dose).

The most common presentation of statin intolerance is myalgia (for example, muscle aches, pains, weakness, or cramps), which can occur in up to 15% of individuals treated with statins. In most cases, the symptoms are mild and are rarely associated with myositis (muscle inflammation) and markers of muscle injury (creatine kinase). Of note, the symptoms are completely reversible shortly after the statin is stopped. Serious muscle damage or rhabdomyolysis associated with statin treatment is extremely rare, for instance, occurring in 1 in 23 million individuals with prescriptions for atorvastatin. Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]). Mild to moderate increases in creatine kinase may occasionally be seen in patients taking statins who have no muscle-related side effects, but this should not be grounds to stop statin therapy.[16]

Appendix B

Simon Broome Register Diagnostic Criteria.[16]

Definite Familial Hypercholesterolemia
Raised cholesterol
--Total cholesterol greater than 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 (aged > 16 years);
AND
--Tendon xanthomas in the patient or in a first (parent, sibling, or child) or second-degree relative (grandparent, aunt, or uncle);
OR
DNA-based evidence of LDL-receptor, familial defective APOB, or PCSK9 mutation.
Possible (or Probable) Familial Hypercholesterolemia
Raised cholesterol
--Total cholesterol greater than 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 (aged > 16 years);
AND
Family history of premature myocardial infarction younger than 50 years of age in second-degree relative or younger than 60 years of age in first-degree relative;
OR
Raised cholesterol

--Total cholesterol greater than 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 (aged > 16 years);
AND
Family history of raised cholesterol > 7.5 mmol (290 mg/dL) in adult first-degree or second-degree relative or > 6.7 mmol/L (260 mg/dL) in child or sibling aged < 16 years.

LDL-C – Low-density lipoprotein cholesterol; LDL – Low-density lipoprotein; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.

Appendix C

Dutch Lipid Network Criteria.[17]

Criteria	Score
Family History	
First-degree relative with known premature coronary and/or vascular disease (men < 55 years, women < 60 years)	1
First degree relative with known LDL-C > 95th percentile for age and sex	1
First-degree relative with tendon xanthomata and/or arcus cornealis, OR	2
Children aged < 18 years with LDL-C > 95th percentile for age and sex	2
Clinical History	
Patient with premature CAD (age as above)	2
Patient with premature cerebral or peripheral vascular disease (age as above)	1
Physical Examination	
Tendon xanthomas	6
Arcus cornealis at age < 45 years	4
LDL-C	
LDL-C ≥ 8.5 mmol/L (330 mg/dL)	8
LDL-C 6.5 to 8.4 mmol/L (250 to 329 mg/dL)	5
LDL-C 5.0 to 6.4 mmol/L (190 to 249 mg/dL)	3
LDL-C 4.0 to 4.9 mg/dL (155 to 189 mg/dL)	1
DNA analysis	
Functional mutation LDLR, APOB or PCSK9 gene	8
Stratification	**Total score**
Definite familial hypercholesterolemia	> 8
Probable familial hypercholesterolemia	6 to 8
Possible familial hypercholesterolemia	3 to 5
Unlikely familial hypercholesterolemia	< 3

LDL-C – Low-density lipoprotein cholesterol; CAD – Coronary artery disease; LDLR – Low-density lipoprotein receptor; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.

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