PRIOR AUTHORIZATION POLICY

POLICY: Proprotein Convertase Subtilisin Kexin Type 9 Inhibitors – Praluent Prior Authorization Policy
- Praluent® (alirocumab subcutaneous injection – Regeneron)

REVIEW DATE: 04/13/2022; selected revision 06/22/2022

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.[17]

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 ≥ 50%. Ezetimibe is usually the next therapy added.

- 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, those with a history of myocardial infarction (MI), stable or unstable angina or coronary or other revascularizations, stroke, transient ischemic attack, or peripheral arterial disease. 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 published guidelines for the screening, diagnosis, and management of pediatric and adult patients with familial hypercholesterolemia** (2011).[8] 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. Other guidelines and reviews note that the addition of a PCSK9 inhibitor to a statin plus ezetimibe regimen can be considered if this goal is not achieved.[5,9]

- 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.[14] 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.[14] Other guidelines note that ezetimibe and PCSK9 inhibitors can be added if further reductions are needed; Juxtapid® (lomitapide capsules) can be considered.[5,10]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Praluent. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and monitoring, approval requires Praluent to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Praluent is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Atherosclerotic Cardiovascular Disease.*** Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has had 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; OR
     - **ii.** Angina (stable or unstable); OR
     - **iii.** A past history of stroke or transient ischemic attack; OR
     - **iv.** Peripheral arterial disease; OR
     - **v.** Patient has undergone a coronary or other arterial revascularization procedure in the past; AND
       Note: Examples include coronary artery bypass graft surgery, percutaneous coronary intervention, angioplasty, and coronary stent procedures.
   - **C)** Patient meets one of the following criteria (i or ii):
     - **i.** Patient meets both of the following (a and b):
       - **a)** Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks; AND
       - **b)** Low-density lipoprotein cholesterol level after this treatment remains ≥ 70 mg/dL; OR
     - **ii.** Patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):
       - **a)** Patient experienced statin-related rhabdomyolysis; OR
         Note: 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]).

b) Patient meets all of the following [(1), (2), and (3)]:

(1) Patient experienced skeletal-related muscle symptoms; AND
Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).

(2) The skeletal-related muscle symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND

(3) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND
Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

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

2. Heterozygous Familial Hypercholesterolemia (HeFH).* Approve for 1 year if the patient meets the following criteria (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Patient meets one of the following criteria (i, ii, or iii):

i. Patient has an untreated low-density lipoprotein cholesterol (LDL-C) level ≥ 190 mg/dL (prior to treatment with antihyperlipidemic agents); OR

ii. Patient has genetic confirmation of heterozygous familial hypercholesterolemia 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; OR

iii. Patient has been diagnosed with heterozygous familial hypercholesterolemia meeting one of the following diagnostic criteria thresholds (a or b):

a) Patient meets both of the following [(1) and (2)]:

(1) Prescriber used the Dutch Lipid Network criteria to diagnose heterozygous familial hypercholesterolemia; AND

(2) Patient has a score > 5; OR

b) Patient meets both of the following [(1) and (2)]:

(1) Prescriber used the Simon Broome criteria to diagnose heterozygous familial hypercholesterolemia; AND

(2) Patient met the threshold for "definite" or "possible (or probable)" familial hypercholesterolemia; AND

C) Patient meets one of the following criteria (i or ii):

i. Patient meets both of the following criteria (a and b):

a) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks; AND

b) LDL-C level after this treatment remains ≥ 70 mg/dL; OR

ii. Patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):

a) Patient experienced statin-related rhabdomyolysis; OR
Note: 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]);

b) Patient meets all of the following [(1), (2), and (3)]:

(1) Patient experienced skeletal-related muscle symptoms; AND
Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).
(2) The skeletal-related muscle symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND
(3) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND
Note: Examples of skeletal-related muscle symptoms include myopathy or myalgia.

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

3. Homozygous Familial Hypercholesterolemia (HoFH).* Approve for 1 year if the patient meets the following criteria (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Patient meets one of the following (i, ii, or iii):

i. Patient 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; OR

ii. Patient has an untreated low-density lipoprotein (LDL-C) level > 500 mg/dL AND meets one of the following (a or b):
Note: Untreated refers to prior therapy with any antihyperlipidemic agent.

a) Patient had clinical manifestations of homozygous familial hypercholesterolemia before 10 years of age; OR
Note: Clinical manifestations of homozygous familial hypercholesterolemia are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas, or xanthelasma.

b) Both parents of the patient had untreated LDL-C levels or total cholesterol levels consistent with heterozygous familial hypercholesterolemia; OR
Note: An example of heterozygous familial hypercholesterolemia in both parents would be if both had an untreated LDL-C level ≥ 190 mg/dL and/or an untreated total cholesterol level > 250 mg/dL.

iii. Patient has a treated LDL-C level ≥ 300 mg/dL AND meets one of the following (a or b):
Note: 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., Repatha [evolocumab subcutaneous injection]), Evkeeza (evinacumab-dgnb intravenous infusion), and Juxtapid (lomitapide capsules).

a) Patient had clinical manifestations of homozygous familial hypercholesterolemia before 10 years of age; OR
Note: Examples of clinical manifestations of homozygous familial hypercholesterolemia are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma.

b) Both parents of the patient had untreated LDL-C levels or total cholesterol levels consistent with heterozygous familial hypercholesterolemia; AND
Note: An example of heterozygous familial hypercholesterolemia in both parents would be if both had an untreated LDL-C ≥ 190 mg/dL and/or an untreated total cholesterol > 250 mg/dL.

C) Patient meets one of the following criteria (i or ii):

i. Patient meets both of the following (a and b):

a) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks; AND
b) LDL-C level after this treatment remains ≥ 70 mg/dL; OR

ii. Patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):
a) Patient experienced statin-related rhabdomyolysis; OR
Note: 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]); OR
b) Patient meets all of the following criteria [(1), (2), and (3)]:
(1) Patient experienced skeletal-related muscle symptoms; AND
Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).
(2) The skeletal-related muscle symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND
(3) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND
Note: Examples of skeletal-related muscle symptoms include myopathy or myalgia.

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

4. Primary Hyperlipidemia.* Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
Note: This is not associated with atherosclerotic cardiovascular disease (ASCVD) or heterozygous familial hypercholesterolemia (HeFH) and may be referred to as combined hyperlipidemia, hypercholesterolemia (pure, primary), dyslipidemia, or increased/elevated low-density lipoprotein cholesterol (LDL-C) levels.
A) Patient is ≥ 18 years of age; AND
B) Patient has a coronary artery calcium or calcification score ≥ 300 Agatston units; AND
C) Patient meets one of the following criteria (i or ii):
i. Patient meets all of the following criteria (a, b and c):
a) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]); AND
b) Patient has tried the one high-intensity statin therapy above along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND
c) LDL-C level after this treatment regimen remains ≥ 100 mg/dL; OR

ii. Patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):
a) Patient experienced statin-related rhabdomyolysis; OR
Note: 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]).
b) Patient meets all of the following [(1), (2), and (3)]:
(1) Patient experienced skeletal-related muscle symptoms; AND

Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness or tenderness).

(2) The skeletal-related muscle symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity combination product); AND

(3) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms (e.g., myopathy, myalgia) resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND

Note: Examples of skeletal-related muscle symptoms include myopathy or myalgia.

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

Note:

* A patient may have a diagnoses that pertain to more than one FDA-approved indication, therefore, consider review under different approval conditions, if applicable (e.g., a patient with heterozygous familial hypercholesterolemia or homozygous familial hypercholesterolemia may have had a clinical ASCVD event, a patient with primary hyperlipidemia may have heterozygous familial hypercholesterolemia).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Praluent is not recommended in the following situations:

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.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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APPENDIX A.

Simon Broome Register Diagnostic Criteria.[15]

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 B.

Dutch Lipid Network Criteria.[16]

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.