Medical Drug Clinical Criteria

Subject: Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) Inhibitor

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Overview

This document addresses the use of proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors including:

- Praluent (alirocumab)
- Repatha (evolocumab)

PCSK9 inhibitors are approved by the Food and Drug Administration (FDA) as adjunctive therapy or alone for the lowering of low-density lipoprotein cholesterol (LDL-C) in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH). PCSK9 inhibitors are also FDA approved for use in individuals with homozygous familial hypercholesterolemia (HoFH) as well as to reduce the risk of cardiovascular events in adults with established cardiovascular disease. Repatha has a pediatric indication for adjunctive therapy in individuals 10 years of age and older with HeFH or HoFH. Praluent has a pediatric indication for adjunctive therapy in individuals 8 years of age and older with HeFH.

Familial hypercholesterolemia is an inherited condition caused by genetic mutations which cause high levels of LDL-C at an early age. There are two types of familial hypercholesterolemia (FH). Heterozygous FH (HeFH) is the more common type occurring in approximately 1 in 200 to 250 individuals. Individuals with HeFH have one altered copy of a cholesterol-regulating gene. Homozygous FH (HoFH) is the rare, more severe form, occurring in approximately 1 in 300,000 to 400,000 individuals. Individuals with HoFH have two altered copies of cholesterol-regulating genes. HoFH can cause LDL-C levels more than six times as high as normal (for example, 650-1,000 mg/dL).

Definitive diagnosis of familial hypercholesterolemia is established by genetic confirmation of one or more mutations in one of the genes critical for LDL-C catabolism. If genetic testing is unavailable, diagnosis can be established though clinical criteria based on LDL-C levels, clinical presentation and family history.

In the clinical setting, statins are considered first-line drug therapy, in addition to healthy lifestyle interventions, in individuals requiring treatment for abnormal cholesterol. Other lipid lowering therapies should be considered second-line options for individuals needing additional cholesterol lowering or who can't tolerate moderate to high doses of statins.

In 2018, the American Heart Association (AHA)/American College of Cardiology (ACC) released guidelines on the management of blood cholesterol. In very high-risk ASCVD, the guidance recommends considering adding non-statins to statin therapy when LDL-C remains greater than or equal to 70 mg/dL. Ezetimibe is the first agent to consider adding on to maximally tolerated statin therapy. PCSK9 inhibitors can be considered for addition if LDL-C remains greater than or equal to 70 mg/dL on statin therapy combined with ezetimibe.

The 2018 AHA/ACC guidelines recommend using an LDL-C threshold of greater than or equal to 100 mg/dL to consider adding non-statins to statin therapy in individuals with severe primary hypercholesterolemia. Ezetimibe is the first non-statin to consider adding to therapy. PCSK9 inhibitors can be considered for addition if LDL-C remains greater than or equal to 100 mg/dL on statin therapy combined with ezetimibe.

In 2022, the ACC released an expert consensus decision pathway on the role of non-statin therapies for LDL-C lowering. In very high-risk ASCVD, the pathway recommends considering adding non-statins to statin therapy when LDL-C remains greater than or equal to 55 mg/dL. Ezetimibe and/or PCSK9 monoclonal antibodies are the first agents to consider adding to statin therapy. Nexletol and Leqvio are secondary options that can be considered for addition. In lower risk ASCVD, the pathway recommends considering adding non-statins to statin therapy when LDL-C remains greater than or equal to 70 mg/dL. The preference for agent addition generally follows the recommendations for individuals at very high risk.

The 2022 pathway recommends using an LDL-C threshold of greater than or equal to 100 mg/dL to consider adding non-statins to statin therapy in individuals without ASCVD but with baseline LDL-C greater than or equal to 190 mg/dL. Ezetimibe and/or PCSK9 monoclonal antibodies are the first agents to consider adding to statin therapy. Nexletol and Leqvio are secondary options that can be considered for addition.

Statins have labeled warnings for liver enzyme abnormalities and skeletal muscle effects including myopathy and rhabdomyolysis. Statin-induced adverse events leading to some degree of intolerance is reported in as many as 5% to 30% of individuals although incidence and prevalence vary. The National Lipid Association (NLA) has provided guidance defining statin intolerance as one or more adverse effects associated with statin therapy, which resolves or improves with dose reduction or discontinuation, and can be classified as complete inability to tolerate any dose of a statin or partial intolerance, with inability to tolerate the dose necessary to achieve the individual-specific therapeutic objective. To classify an individual as having statin intolerance, a minimum of two statins should have been attempted, including at least one at the lowest approved daily dosage.

The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial sought to assess the outcome benefit of Repatha compared with placebo when added to an optimized regimen of cholesterol-lowering medication (statin with or without ezetimibe). The trial enrolled more than 27,000 patients with a history of cardiovascular disease at high-risk for a recurrent event. The trial met its primary endpoint, a composite measure of cardiovascular outcomes that included reductions in cardiovascular deaths, heart attacks, strokes, placement of stents and hospitalizations, resulting in an absolute reduction of 1.5% after 26 months of Repatha. This translates to the need to treat 74 patients with Repatha for 2 years to prevent one cardiovascular death, myocardial infarction or stroke. Repatha had no observed effect on cardiovascular mortality as an individual endpoint.

The ODYSSEY Outcomes trial sought to evaluate the effect of Praluent compared with placebo when added to an optimized regimen of cholesterol-lowering medication (statin with or without ezetimibe). The trial enrolled approximately 18,000 individuals with a recent history of acute myocardial infarction or unstable angina. The trial met its primary endpoint demonstrating Praluent lowered the absolute risk of composite CHD death or non-fatal MI or fatal/non-fatal ischemic stroke or unstable angina requiring hospitalization by 1.6 % after 34 months. This translates to the need to treat 63 patients with Praluent for approximately 34 months to prevent one cardiovascular events. Praluent had no observed effect on cardiovascular mortality as an individual endpoint.

World Health Organization (WHO)/Dutch Lipid Clinic Network Criteria for Familial Hypercholesterolemia (FH) Diagnosis

Criteria	Points
Family History	
Known premature coronary and vascular disease (men <55 years, women <60 years) in first degree relative	1
Known LDL-C >95th percentile in first degree relative	1
Tendon xanthoma and/or corneal arcus in first degree relative	2
Children aged <18 years with LDL-C >95th percentile	2
Personal Clinical History	
Premature coronary artery disease (men <55 years, women <60 years)	2
Premature cerebral or peripheral vascular disease (men <55 years, women <60 years)	1
Clinical Exam	
Tendon xanthoma	6
Corneal arcus in individual aged <45 years	4
LDL-C Level	

> 329 mg/dL (>8.5 mmol/L)	8
250-329 mg/dL (6.5-8.4 mmol/L)	5
190-249 mg/dL (5.0-6.4 mmol/L)	3
155-189 mg/dL (4.0-4.9 mmol/L)	1
Genetic Testing	
Functional mutation in LDLR, ApoB or PCSK9 gene	8

Scoring: Definite FH:> 8 points; Probable FH: 6-8 points; Possible FH: 3-5 points; Unlikely FH: 0-2 points

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Repatha (evolocumab)

Initial requests for Repatha (evolocumab) may be approved when the following criteria are met:

I. Individual is at high risk for atherosclerotic cardiovascular disease (ASCVD) events as identified by one of the following:
   A. Individual has Homozygous Familial Hypercholesterolemia (HoFH) verified by (Cuchel 2023):
      1. Presence of two mutant alleles at the LDLR, apoB, PCSK9 or ARH adaptor protein (LDLRAP1) gene locus; **OR**
      2. An untreated LDL-C concentration greater than 400 mg/dL (10 mmol/L) **AND one** of the following:
         a. Cutaneous or tendonous xanthoma before age of 10 years; **OR**
         b. Untreated LDL-C levels consistent with heterozygous familial hypercholesterolemia in both parents (greater than 190 mg/dL); **OR**
   B. Individual has Heterozygous Familial Hypercholesterolemia (HeFH) verified by (Singh 2015, WHO 1999):
      1. Presence of a mutation in LDLR, ApoB, or PCSK9, ARH adaptor protein (LDLRAP1) gene; **OR**
      2. WHO/Dutch Lipid Clinic Network criteria with score of greater than eight points; **OR**
   C. Individual has a history of clinical atherosclerotic cardiovascular disease ASCVD, including one or more of the following (AHA/ACC 2018):
      1. Acute coronary syndrome;
      2. Coronary artery disease (CAD);
      3. History of myocardial infarction (MI);
      4. Stable or unstable angina;
      5. Coronary or other arterial revascularization;
      6. Stroke;
      7. Transient ischemic attack (TIA);
      8. Peripheral arterial disease (PAD); **OR**
   D. Individual has primary hyperlipidemia;

AND

II. Individual meets one of the following:
   A. Individual is on high intensity statin therapy or statin therapy at the maximum tolerated dose (high intensity statin is defined as atorvastatin 40 mg or higher or rosuvastatin 20 mg or higher) (AHA/ACC 2018); **OR**
   B. Individual is statin intolerant based on one of the following:
      1. Inability to tolerate at least two statins, with at least one started at the lowest starting daily dose, demonstrated by adverse effects associated with statin therapy that resolve or improve with dose reduction or discontinuation (NLA 2022); **OR**
      2. Statin associated rhabdomyolysis or immune-mediated necrotizing myopathy (IMNM) after a trial of one statin; **OR**
   C. Individual has a contraindication for statin therapy including but not limited to active liver disease, unexplained persistent elevation of hepatic transaminases, or pregnancy;

AND

III. Individual, excluding HoFH, has achieved suboptimal lipid lowering response despite at least 90 days of compliant lipid lowering therapy and lifestyle modifications as defined (AHA/ACC 2018, ACC 2022):
    A. For individuals where initial LDL-C is known:
        1. Less than 50% reduction in LDL-C; **OR**
    B. For individuals where initial LDL-C is unknown:
        1. ASCVD and LDL-C remains greater than or equal to 55 mg/dL; **OR**
        2. No history of ASCVD and LDL-C remains greater than or equal to 100 mg/dL.

Continuation requests for Repatha (evolocumab) may be approved when the following criteria are met:

I. Individual continues to use in combination with maximally tolerated statin therapy (unless contraindication or individual is statin intolerant); **AND**
II. Individual has achieved LDL reduction.

Repatha (evolocumab) may not be approved for the following:

I. Use in combination with Leqvio or Praluent; **OR**
II. May not be approved when the above criteria are not met and for all other indications.

Initial Approval Duration: 1 year
Continuation Approval Duration: 1 year

Praluent (alirocumab)

Initial requests for Praluent (alirocumab) may be approved when the following criteria are met:

I. Individual is at high risk for atherosclerotic cardiovascular disease (ASCVD) events as identified by one of the following:
    A. Individual has Homozygous Familial Hypercholesterolemia (HoFH) verified by (Cuchel 2023):
        1. Presence of two mutant alleles at the LDLR, apoB, PCSK9 or ARH adaptor protein (LDLRAP1) gene locus; **OR**
        2. An untreated LDL-C concentration greater than 400 mg/dL (10 mmol/L) **AND one** of the following:
            a. Cutaneous or tendonous xanthoma before age of 10 years; **OR**
            b. Untreated LDL-C levels consistent with heterozygous familial hypercholesterolemia in both parents (greater than 190 mg/dL); **OR**
    B. Individual has Heterozygous Familial Hypercholesterolemia (HeFH) verified by (Singh 2015, WHO 1999):
        1. Presence of a mutation in LDLR, ApoB, PCSK9 or ARH adaptor protein (LDLRAP1) gene; **OR**
        2. WHO/Dutch Lipid Clinic Network criteria with score of greater than eight points; **OR**
    C. Individual has a history of clinical atherosclerotic cardiovascular disease (ASCVD), including one or more of the following (AHA/ACC 2018):
        1. Acute coronary syndrome;
        2. Coronary artery disease (CAD);
        3. History of myocardial infarction (MI);
        4. Stable or unstable angina;
        5. Coronary or other arterial revascularization;
        6. Stroke;
        7. Transient ischemic attack (TIA);
        8. Peripheral arterial disease (PAD); **OR**
    D. Individual has primary hyperlipidemia;

AND

II. Individual meets one of the following:
    A. Individual is on high intensity statin therapy or statin therapy at the maximum tolerated dose (high intensity statin is defined as atorvastatin 40 mg or higher or rosuvastatin 20 mg or higher) (AHA/ACC 2018); **OR**
    B. Individual is statin intolerant based on one of the following:

1. Inability to tolerate at least two statins, with at least one started at the lowest starting daily dose, demonstrated by adverse effects associated with statin therapy that resolve or improve with dose reduction or discontinuation (NLA 2022); **OR**
2. Statin associated rhabdomyolysis or immune-mediated necrotizing myopathy (IMNM) after a trial of one statin; **OR**

C. Individual has a contraindication for statin therapy including but not limited to active liver disease, unexplained persistent elevation of hepatic transaminases, or pregnancy;

AND

III. Individual, excluding HoFH, has achieved suboptimal lipid lowering response despite at least 90 days of compliant lipid lowering therapy and lifestyle modifications as defined (AHA/ACC 2018, ACC 2022):
- A. For individuals where initial LDL-C is known:
  1. Less than 50% reduction in LDL-C; **OR**
- B. For individuals where initial LDL-C is unknown:
  1. ASCVD and LDL-C remains greater than or equal to 55 mg/dL; **OR**
  2. No history of ASCVD and LDL-C remains greater than or equal to 100 mg/dL.

Continuation requests for Praluent (alirocumab) may be approved when the following criteria are met:

I. Individual continues to use in combination with maximally tolerated statin therapy (unless contraindication or individual is statin intolerant); **AND**
II. Individual has achieved LDL reduction.

Praluent (alirocumab) may not be approved for the following:

I. Use in combination with Leqvio or Repatha; **OR**
II. May not be approved when the above criteria are not met and for all other indications.

Initial Approval Duration: 1 year
Continuation Approval Duration: 1 year

Quantity Limits

PCSK9 Inhibitor Quantity Limits

Drug	Limit
Praluent (alirocumab) 75 mg/ml pen,150 mg/ml syringe or pen	2 or pens per 28 days
Repatha (evolocumab) 140 mg/ml prefilled syringe or auto-injector	2 prefilled syringes or auto-injectors per 28 days
Repatha (evolocumab) 420 mg/3.5 ml prefilled cartridge	1 prefilled cartridge per 28 days
Override Criteria	
For individuals with homozygous familial hypercholesterolemia (HoFH), may approve 2 Repatha 420 mg/3.5 mL prefilled cartridges per 28 days for the following: 1. Individual has tried Repatha 420 mg per 28 days for 12 weeks and not achieved adequate LDL-C reduction; **OR** 2. Individual is on lipid apheresis.	

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J3490	Unclassified drug [when specified as alirocumab (Praluent) or evolocumab (Repatha)]
J3590	Unclassified biologics [when specified as alirocumab (Praluent) or evolocumab (Repatha)]

C9399	Unclassified drugs or biologics (when specified as alirocumab (Praluent) or evolocumab [Repatha])

ICD-10 Diagnosis

E78.00	Pure hypercholesterolemia, unspecified
E78.01	Familial hypercholesterolemia
E78.1	Pure hyperglyceridemia
E78.2	Mixed hyperlipidemia
E78.41-E78.5	Other and unspecified hyperlipidemia
G45.0-G45.9	Transient cerebral ischemic attacks and related syndromes
I20.0-I20.9	Angina pectoris
I21.01-I21.B	Acute myocardial infarction
I22.0-I22.9	Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction
I23.7	Postinfarction angina
I24.0-I24.9	Other acute ischemic heart diseases
I25.10-I25.9	Chronic ischemic heart disease
I63.00-I63.9	Cerebral infarction
I65.01-I65.9	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
I66.01-I66.9	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
I67.2	Cerebral atherosclerosis
I67.82	Cerebral ischemia
I69.00-I69.998	Sequelae of cerebrovascular disease
I70.0-I70.92	Atherosclerosis
I73.9	Peripheral vascular disease, unspecified
Z83.42	Family history of familial hypercholesterolemia
Z86.73	Personal history of transient ischemic attack (TIA), and cerebral infarction without residual deficits
Z95.1	Presence of aorto coronary bypass graft
Z95.5	Presence of coronary angioplasty implant and graft
Z95.820-Z95.828	Presence of other vascular implants and grafts
Z98.61	Coronary angioplasty status
Z98.62	Peripheral vascular angioplasty status

Document History

Revised: 2/21/2025
Document History:

- 2/21/2025 – Select Review: Revise primary hyperlipidemia criteria. Coding Reviewed: No changes.
- 8/16/2024 – Annual Review: Update criteria with additional primary hyperlipidemia indication; update homozygous familial hypercholesterolemia diagnosis criteria. Coding Reviewed: Changed coding description for ICD-10-CM E78.41-E78.5, and expanded I21.01-I21.A9 to I21.01-I21.B.
- 11/17/2023 – Select Review: Update criteria by removing step through ezetimibe; update LDL-C requirement for individuals with history of ASCVD; extend initial approval duration. Coding Reviewed: No changes.
- 8/18/2023 – Annual Review: Wording and formatting changes. Coding Reviewed: No changes.
- 8/19/2022 – Annual Review: Update statin intolerance criteria. Wording and formatting changes. Coding Reviewed: No changes.
- 3/14/2022 – Select Review: Update clinical criteria to exclude concurrent use with Leqvio. Coding Reviewed: Added HCPCS C9399.

- 8/20/2021 – Annual Review: Update statin intolerance criteria; update may not approve criteria to remove exclusion for use with Juxtapid and add exclusion for concomitant PCSK9 therapy. Add override criteria to Repatha quantity limit for new HoFH dosing regimen. Remove Praluent prefilled syringes as obsolete. Update guideline references. Coding reviewed: No changes.
- 8/21/2020 – Annual Review: Clarify approval duration for Praluent and Repatha clinical criteria. Remove reference to Kynamro as agent is obsolete. Wording and formatting changes. Administrative update to add drug specific quantity limit. Coding reviewed: No changes.
- 08/16/2019 – Annual Review: Wording and formatting changes. Coding Reviewed: No changes.
- 02/22/2019 – Select Review: Reference update.
- 08/17/2018 – Annual Review: Initial review of Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) Inhibitor Clinical Criteria. Simplify statin intolerance criteria. Remove age criteria. Add exception to lipid level criteria for HoFH for Praluent to mirror Repatha. Update continuation criteria. Remove documentation language. Add references to non-label-based criteria elements. Wording and formatting updates for consistency and clarification. Coding review: No changes. Coding update adding E78.41 and E78.49 already reflected on document. Criteria is less restrictive, but dx still applies.

References

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Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.