Clinical Policy: Alirocumab (Praluent)

Reference Number: ERX.SPA.168
Effective Date: 01.11.17
Last Review Date: 02.21
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Alirocumab (Praluent®) is a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor antibody.

FDA Approved Indication(s)
Praluent is indicated:

- To reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease
- 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 (including heterozygous familial hypercholesterolemia [HeFH]) to reduce low-density lipoprotein cholesterol (LDL-C)

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Praluent is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Primary Hyperlipidemia (including HeFH) and Atherosclerotic Cardiovascular Disease (must meet all)**:**

1. Diagnosis of one of the following (a or b):
   a. Primary hyperlipidemia with both of the following (i and ii) (note: these criteria in section I.A.1.a do not apply to HeFH. Refer to section I.A.2 below for coverage criteria for HeFH);
      i. Documentation of one of the following (a or b):
         a) Presence of a genetically mediated form of primary hyperlipidemia as evidenced by confirmatory genetic testing results;
         b) A diagnosis of secondary hyperlipidemia has been ruled out with absence of all of the following potential causes of elevated cholesterol (a-f):
            a) Poor diet;
            b) Hypothyroidism;
            c) Obstructive liver disease;
            d) Renal disease;
            e) Nephrosis;
            f) Medications that have had a clinically relevant contributory effect on the current degree of the member's elevated lipid levels including, but not limited to: glucocorticoids, sex hormones, antipsychotics, antiretrovirals, immunosuppressive agents, retinoic acid derivatives;
      ii. Baseline LDL-C (prior to any lipid-lowering pharmacologic therapy) was one of the following (a or b):
         a) ≥ 190 mg/dL for genetically mediated primary hyperlipidemias;
         b) ≥ 220 mg/dL for non-genetically mediated primary hyperlipidemias;

b. Atherosclerotic cardiovascular disease (ASCVD) as evidenced by a history of any one of the following conditions (i-vii):
   i. Acute coronary syndromes;
   ii. Clinically significant coronary heart disease (CHD) diagnosed by invasive or noninvasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography, or nuclear imaging);
   iii. Coronary or other arterial revascularization;
   iv. Myocardial infarction;
   v. Peripheral arterial disease presumed to be of atherosclerotic origin;
   vi. Stable or unstable angina;
   vii. Stroke or transient ischemic attack (TIA);

2. For members with HeFH, both of the following are met (a and b):
   a. Baseline LDL-C (prior to any lipid-lowering pharmacologic therapy) was ≥ 190 mg/dL;
   b. HeFH diagnosis is confirmed by one of the following (i or ii):
      i. World Health Organization (WHO)/Dutch Lipid Network familial hypercholesterolemia diagnostic criteria score of > 8 as determined by requesting provider (*see Appendix D*);
      ii. Definite diagnosis per Simon Broome criteria (*see Appendix D*);
3. Member does not have a diagnosis of homozygous familial hypercholesterolemia (HoFH);
4. Prescribed by or in consultation with a cardiologist, endocrinologist, or lipid specialist;
5. Age ≥ 18 years;
6. For members on statin therapy, both of the following (a and b):
   a. Praluent is prescribed in conjunction with a statin at the maximally tolerated dose;
   b. Member has been adherent for at least the last 4 months to maximally tolerated doses of one of the following statin regimens (i, ii, or iii):
      i. A high intensity statin (*see Appendix E*);
      ii. A moderate intensity statin (*see Appendix E*), and member has one of the following (a or b):
         a) Intolerance to two high intensity statins;
         b) A statin risk factor (*see Appendix G*);
      iii. A low intensity statin, and member has one of the following (a or b):
         a) Intolerance to one high and one moderate intensity statins;
         b) A statin risk factor (*see Appendix G*) and history of intolerance to two moderate intensity statins;
7. For members not on statin therapy, member meets one of the following (a or b):
   a. Statin therapy is contraindicated per Appendix F;
   b. For members who are statin intolerant, member has tried at least two statins, one of which must be hydrophilic (pravastatin, fluvastatin, or rosuvastatin), and member meets one of the following (i or ii):
      i. Member has documented statin risk factors (*see Appendix G*);
      ii. Member is statin intolerant due to statin-associated muscle symptoms (SAMS) and meets both of the following (a and b):
         a) Documentation of intolerable SAMS persisting at least two weeks, which disappeared with discontinuing the statin therapy and recurred with a statin re-challenge;
         b) Documentation of re-challenge with titration from lowest possible dose and/or intermittent dosing frequency (e.g., 1 to 3 times weekly);
8. Member has been adherent to ezetimibe therapy used concomitantly with a statin at the maximally tolerated dose for at least the last 4 months, unless contraindicated per Appendix F or member has a history of ezetimibe intolerance (e.g., associated diarrhea or upper respiratory tract infection);
9. Documentation of recent (within the last 60 days) LDL-C of one of the following (a, b, or c):
   a. ≥ 70 mg/dL for ASCVD;
   b. ≥ 100 mg/dL for genetically mediated severe primary hyperlipidemia (including HeFH);
   c. ≥ 130 mg/dL for non-genetically mediated severe primary hypercholesterolemia;
10. Treatment plan does not include coadministration with Juxtapid®, Kynamro®, or Repatha;

11. Dose does not exceed 75 mg every 2 weeks or 300 mg per month.

Approval duration:
Commercial – 6 months
Medicaid – 3 months

B. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Primary Hyperlipidemia (including HeFH) and Atherosclerotic Cardiovascular Disease (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. If statin tolerant, documentation of adherence to a statin at the maximally tolerated dose;
3. Member meets one of the following (a or b):
   a. Request is for 75 mg every 2 weeks or 300 mg per month, and lab results within the last 3 months are submitted showing an LDL-C reduction since initiation of Praluent therapy;
   b. Request is for 150 mg every 2 weeks and one of the following (i or ii):
      i. If request represents a new dose increase, member has demonstrated adherence to Praluent and, if applicable, ezetimibe and/or statin therapies, and lab results within the last 3 months are submitted showing an LDL-C > 70 mg/dL after a minimum of 8 weeks of Praluent therapy at 75 mg;
      ii. If request represents a continuation of Praluent 150 mg, lab results within the last 3 months show an LDL-C reduction since initiation of the Praluent dose increase.

Approval duration:
Commercial – 12 months *(6 months if request is for dose increase)*
Medicaid – 12 months *(3 months if request is for dose increase)*

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ACC/AHA: American College of Cardiology/American Heart Association
ALT: alanine transaminase
apoB: apolipoprotein B
ASCVD: atherosclerotic cardiovascular disease
CHD: coronary heart disease
FDA: Food and Drug Administration
FH: familial hypercholesterolemia
HeFH: heterozygous familial hypercholesterolemia
HoFH: homozygous familial hypercholesterolemia
LDL-C: low density lipoprotein cholesterol
LDLR: low density lipoprotein receptor
PCSK9: proprotein convertase subtilisin kexin 9
SAMS: statin-associated muscle symptoms
TIA: transient ischemic attack
WHO: World Health Organization

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
ezetimibe/simvastatin (Vytorin®)	10/40 mg PO QD	10 mg-40 mg/day (use of the 10/80 mg dose is restricted to patients who have been taking simvastatin 80 mg for ≥ 12 months without evidence of muscle toxicity)
ezetimibe (Zetia®)	10 mg PO QD	10 mg/day
atorvastatin (Lipitor®)	40 mg PO QD	80 mg/day
rosuvastatin (Crestor®)	5 - 40 mg PO QD	40 mg/day
Repatha® (evolocumab)	140 mg SC Q2 weeks or 420 mg SC once monthly	420 mg/month

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings
- Contraindication(s): history of serious hypersensitivity reaction to Praluent
- Boxed warning(s): none

Appendix D: Criteria for Diagnosis of HeFH
- Dutch Lipid Clinic Network criteria for Familial Hypercholesterolemia (FH):

FH Criteria	Points	Member's Score†
Family History		
First-degree relative with known premature* coronary and vascular disease	1	Place highest score here (0, 1 or 2)
First-degree relative with known LDL-C level above the 95th percentile	1	
First-degree relative with tendinous xanthomata and/or arcus cornealis	2	
Children aged < 18 years with LDL-C level above the 95th percentile	2	
Clinical History		
Patient with premature* coronary artery disease	2	Place highest score here (0, 1 or 2)
Patient with premature* cerebral or peripheral vascular disease	1	
Physical Examination		
Tendinous xanthomata	6	Place highest score here (0, 4 or 6)
Arcus cornealis prior to age 45 years	4	
Cholesterol Levels - mg/dL (mmol/liter)		
LDL-C ≥330 mg/dL (≥8.5)	8	Place highest score here (0, 1, 3, 5 or 8)
LDL-C 250 – 329 mg/dL (6.5 – 8.4)	5	
LDL-C 190 – 249 mg/dL (5.0 – 6.4)	3	
LDL-C 155 – 189 mg/dL (4.0 – 4.9)	1	
DNA Analysis		
Functional mutation in the *LDLR, apo B* or *PCSK9* gene	8	Place highest score here (0 or 8)
TOTAL SCORE	Definite FH: >8	Place score total here __

*Premature – men < 55 years or women < 60 years

†Choose the highest score from each of the five categories and then add together for a total score. The five categories are 1) Family History, 2) Clinical History, 3) Physical Examination, 4) Cholesterol Levels, and 5) DNA Analysis.

- Simon Broome Register Group Definition of Definite FH (meets 1 and 2):
  1. One of the following (a or b):
     a. Total cholesterol level above 7.5 mmol/L (290 mg/dL) in adults or a total cholesterol level above 6.7 mmol/L (260 mg/dL) for children under 16
     b. LDL levels above 4.9 mmol/L (190 mg/dL) in adults (4.0 mmol/L in children) (either pre-treatment or highest on treatment)
  2. One of the following (a or b):
     a. Tendinous xanthomas in patient or relative (parent, child, sibling, grandparent, aunt, uncle)
     b. DNA-based evidence of an LDL receptor mutation or familial defective apo B-100
- High and Moderate Risk of ASCVD:
  - Patients with high risk of ASCVD include the following:
    - History of clinical atherosclerotic cardiovascular disease (as defined in section II)
    - Diabetes with an estimated 10-year ASCVD risk ≥ 7.5% for adults 40-75 years of age
    - Untreated LDL ≥ 190 mg/dL
  - Patients with moderate risk of ASCVD include the following:
    - Diabetes with an estimated 10-year ASCVD risk < 7.5% for adults 40-75 years of age
    - Estimated 10-year ASCVD risk ≥ 5% for adults 40-75 years of age
  - The calculator for the 10-year ASCVD risk estimator can be found here: http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate. Information needed to complete the ASCVD Risk Estimator include: gender, race (white, African American, other), systolic blood pressure, history of diabetes, age, total cholesterol, HDL-cholesterol, treatment for hypertension, smoking history or status, and concurrent statin or aspirin therapy.

Appendix E: High and Moderate Intensity Daily Statin Therapy for Adults

High Intensity Statin Therapy ***Daily dose shown to lower LDL-C, on average, by approximately ≥ 50%***
• Atorvastatin 40-80 mg • Rosuvastatin 20-40 mg
Moderate Intensity Statin Therapy ***Daily dose shown to lower LDL-C, on average, by approximately 30% to 50%***
• Atorvastatin 10-20 mg • Fluvastatin XL 80 mg • Fluvastatin 40 mg BID • Lovastatin 40 mg • Pitavastatin 1-4 mg • Pravastatin 40-80 mg • Rosuvastatin 5-10 mg • Simvastatin 20-40 mg
Low Intensity Statin Therapy ***Daily dose shown to lower LDL-C, on average, by < 30%***
• Simvastatin 10 mg • Pravastatin 10-20 mg • Lovastatin 20 mg • Fluvastatin 20-40 mg

Appendix F: Statin and Ezetimibe Contraindications

Statins
• Decompensated liver disease (development of jaundice, ascites, variceal bleeding, encephalopathy) • Laboratory-confirmed acute liver injury or rhabdomyolysis resulting from statin treatment • Pregnancy, actively trying to become pregnant, or nursing

Statins
• Immune-mediated hypersensitivity to the HMG-CoA reductase inhibitor drug class (statins) as evidenced by an allergic reaction occurring with at least TWO different statins
Ezetimibe
• Moderate or severe hepatic impairment [Child-Pugh classes B and C] • Hypersensitivity to ezetimibe (e.g., anaphylaxis, angioedema, rash, urticaria)

Appendix G: Statin Risk Factors

Statin Risk Factors
• Multiple or serious comorbidities, including impaired renal or hepatic function • Unexplained alanine transaminase (ALT) elevations > 3 times upper limit of normal, or active liver disease • Concomitant use of drugs adversely affecting statin metabolism • Age > 75 years, or history of hemorrhagic stroke • Asian ancestry

Appendix H: General Information

- FDA Endocrinologic and Metabolic Drugs Advisory Committee briefing documents for Praluent discuss the questionable determination of statin intolerance, stating: “Many patients who are not able to take statins are not truly intolerant of the pharmacological class.”
- Patients should remain on concomitant therapy with a statin if tolerated due to the established long term cardiovascular benefits.
- Examples of genetically mediated primary hyperlipidemia include but are not limited to the following:
  - Familial hypercholesterolemia
  - Familial combined hyperlipidemia (FCHL)
  - Polygenic hypercholesterolemia
  - Familial dysbetalipoproteinemia
- The diagnosis of SAMS is often on the basis of clinical criteria. Typical SAMS include muscle pain and aching (myalgia), cramps, and weakness. Symptoms are usually bilateral and involve large muscle groups, including the thigh, buttock, back, and shoulder girdle musculature. In contrast, cramping is usually unilateral and may involve small muscles of the hands and feet. Symptoms may be more frequent in physically active patients. Symptoms often appear early after starting stain therapy or after an increase in dose and usually resolve or start to dissipate within weeks after cessation of therapy, although it may take several months for symptoms to totally resolve. Persistence of symptoms for more than 2 months after drug cessation should prompt a search for other causes or for underlying muscle disease possibly provoked by statin therapy. The reappearance of symptoms with statin rechallenge and their disappearance with drug cessation offers the best evidence that the symptoms are truly SAMS.
- Pravastatin, fluvastatin, and rosuvastatin are hydrophilic statins which have been reported to confer fewer adverse drug reactions than lipophilic statins.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Primary hyperlipidemia (including HeFH) or hypercholesterolemia with ASCVD	75 mg SC once every 2 weeks or 300 mg SC once every 4 weeks If response to 75 mg every 2 weeks or 300 mg every 4 weeks is inadequate, dose may be increased to 150 mg once every 2 weeks.	300 mg/month
HeFH undergoing LDL apheresis	150 mg SC every 2 weeks	300 mg/month

VI. Product Availability

Single-use pre-filled pens and syringes: 75 mg/mL, 150 mg/mL

VII. References

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Reviews, Revisions, and Approvals	Date	P&T Approval Date
4Q17 annual review: Converted to new template; Added clinically significant coronary heart disease (CHD) diagnosed by invasive or noninvasive testing as documentation of ASCVD; Changed LDL level from ≥ 70 mg/dL to ≥ 100 mg/dL; Added Simon Broome criteria for diagnosis of HeFH; Added	10.03.17	11.17

Reviews, Revisions, and Approvals	Date	P&T Approval Date
requirement of trial of at least 2 of the hydrophilic statins associated with less ADEs (pravastatin, fluvastatin, or rosuvastatin); Increased initial approval duration from 3 to 6 months to allow for buffer (member picking up med, learning how to self-inject, and going back to MD for re-evaluation); Added use in conjunction with max tolerated statin; Coadministration with Juxtapid (lomitapid), Kynamro (mipomersen), or Repatha (evolocumab) moved to section III from section I; Removed therapeutic life style changes since it's not objectively measured; Specified LDL-C reduction required at re-authorization; Added re-direction to Repatha per formulary.		
3Q 2018 annual review: lowered minimum LDL value required for initial approval from 100 mg/dL to 70 mg/dL; revised trial of ezetimibe language by requiring concomitant statin; added hydrophilic statin with intermittent dosing requirement; moved requirement against coadministration with Juxtapid, Kynamro, Repatha from section III to initial approval criteria; removed specific LDL cut off for continued approval; references reviewed and updated.	05.22.18	08.18
1Q 2019 annual review: no significant changes; references reviewed and updated.	11.20.18	02.19
Criteria updated to include new FDA indication: primary hyperlipidemia (including but not limited to HeFH); FDA indication section updated to include new indication to reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease (note: no change to existing policy for this patient population); concomitant statin usage section modified to more clearly delineate between patients who are currently on statin therapy vs. those who are not, and for the latter, to require documentation of a prior trial of four statins (vs. just two) with documentation of statin risk factors or intolerance; criteria for statin-rechallenge in the setting of SAMS are added; added 3 month initial approval duration for Medicaid (commercial approval duration remains the same); references reviewed and updated.	07.23.19	08.19
Policy updated based on specialist feedback: removed the requirement for explicit documentation of rule out of secondary causes of hyperlipidemia; clarified the requirement for ruling out lipid-increasing medications as a secondary cause of hyperlipidemia, by specifying that the medication must be ruled out only if it has significantly increased the member's lipid levels; increased the timeframe for LDL-C lab draws from 30 days to 60 days; modified the requirement for four prior statin trials to three prior statin trials.	09.19.19	11.19
1Q 2020 annual review: modified requirement for statin intolerance to one high and one moderate intensity statins (previously required two of each) for members on a low intensity statin; modified the requirement for three prior statin trials to two prior statin trials for members not on statin therapy; Appendix E updated based on 2018 ACC/AHA guidelines; references reviewed and updated.	11.05.19	02.20
1Q 2021 annual review: removed HoFH from diagnoses not covered based on positive results from ODYSSEY HoFH study; removed redirection to Repatha based on formulary status (500: NF; 550: preferred); references reviewed and updated.	11.02.20	02.21

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status;

evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.