Clinical Policy: Alirocumab (Praluent)

Reference Number: PA.CP.PHAR.124
Effective Date: 01/2018
Last Review Date: 01/19 Revision Log

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

FDA Approved Indication(s)
Praluent is indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C).

Limitation(s) of use: The effect of Praluent on cardiovascular morbidity and mortality has not been determined.

Policy/Criteria
It is the policy of health plans affiliated with Pennsylvania Health and Wellness that Praluent is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Heterozygous Familial Hypercholesterolemia and Atherosclerotic Cardiovascular Disease (must meet all):

1. Diagnosis of one of the following (a or b):
   a. HeFH as defined 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*);
   b. 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. Prescribed by or in consultation with a cardiologist, endocrinologist or lipid specialist;
3. Age ≥ 18 years;
4. Documentation of recent (within the last 30 days) LDL-C ≥ 70 mg/dL;

5. Member has been adherent to a high intensity statin (*see Appendix E*) regimen for at least the last 4 months, unless one of the following applies (a, b, or c):
   a. Statin therapy is contraindicated per Appendix F;
   b. Member has been adherent to a moderate intensity statin (*see Appendix E*) regimen for at least the last 4 months due to one of the following (i or ii):
      i. Intolerance to two high intensity statins;
      ii. A statin risk factor (*see Appendix G*);
   c. Member is unable to take a high or moderate intensity statin due to one of the following (i or ii):
      i. Intolerance to two high and two moderate intensity statins;
      ii. A statin risk factor (*see Appendix G*) and history of intolerance to two moderate intensity statins;
6. Member meets one of the following (a or b):
   a. Use is in conjunction with a statin at the maximally tolerated dose;
   b. For members not on statin therapy (statin intolerant), member has tried at least two of the hydrophilic statins (i.e., pravastatin, fluvastatin, rosuvastatin) titrated from lowest possible dose at intermittent dosing frequency (e.g., 1 to 3 times weekly);
7. 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);
8. Treatment plan does not include coadministration with Juxtapid®, Kynamro®, Repatha®;
9. Dose does not exceed 75 mg every 2 weeks or 300 mg per month.

Approval duration: 3 months

B. Other diagnoses/indications: Refer to PA.CP.PMN.53.

II. Continued Approval

A. Heterozygous Familial Hypercholesterolemia and Atherosclerotic Cardiovascular Disease Primary Hyperlipidemia (must meet all)**:**

1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
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 every 4 weeks 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 or modification, 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 every 2 weeks or 300 mg every 4 weeks;

ii. If request represents a continuation of Praluent 150 mg, lab results within the last 3 months are submitted showing an LDL-C reduction since initiation of the Praluent dose increase or modification;

Approval duration: 12 months *(3 months if request is for dose increase)*

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy; or
2. Refer to PA.CP.PMN.53

Background

Description/Mechanism of Action:

Alirocumab is a human monoclonal antibody (IgG1 isotype) directed against proprotein convertase subtilisin kexin 9 (PCSK9). Alirocumab binds to PCSK9 and inhibits circulating PCSK9 from binding to the LDL receptor (LDLR) preventing PCSK9-mediated LDLR degradation and permitting LDLR to recycle back to the liver cell surface. By inhibiting the binding of PCSK9 to LDLR, alirocumab increases the number of LDLRs available to clear LDL from the blood, thereby lowering LDL-C levels. Alirocumab is produced by recombinant DNA technology in Chinese hamster ovary cell suspension culture.

Formulations:

Praluent 75/mg/mL or 150 mg/mL solution for subcutaneous injection in a single-dose pre-filled pen or single-dose pre-filled syringe; sterile, preservative free, latex free.

III. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ALT: Alanine transaminase
apo B: apolipoprotein B
ASCVD: atherosclerotic cardiovascular disease
CHD: coronary heart disease
FDA: Food and Drug Administration
FH: familial hypercholesterolemia
HeFH: heterozygous familial hypercholesterolemia
LDL-C: low density lipoprotein cholesterol
LDLR: low density lipoprotein receptor
PCSK9: proprotein convertase subtilisin kexin 9
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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
		simvastatin 80 mg for 12 months or more 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 to 40 mg PO QD	40 mg/day

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 *low density lipoprotein receptor (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.cardiosource.org/ASCVD-Risk-Estimator/. Information needed to complete the ASCVD Risk Estimator include: gender, race (white, African American, other), systolic blood pressure, diabetes, age, total cholesterol, HDL-Cholesterol, treatment for hypertension, current smoker.

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 10-20mg • Fluvastatin XL 80 mg • Fluvastatin 40 mg 2x/day • Lovastatin 40 mg • Pitavastatin 2-4 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 • Pitavastatin 1 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 • 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.

IV. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Hypercholesterolemia with ASCVD	75 mg SC once every 2 weeks or 300 mg SC once every 4 weeks	300 mg/month

Indication	Dosing Regimen	Maximum Dose
	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.	

V. Product Availability
Single-use pre-filled pen, syringe: 75 mg/mL, 150 mg/mL

Reviews, Revisions, and Approvals	Date	Approval Date
Aligned definition of ASCVD with commercial by addition of acute coronary syndrome and clinically significant CHD; aligned trial of Zetia language with commercial by requiring concomitant statin; added hydrophilic statin with intermittent dosing requirement; references reviewed and updated.	05.18	
1Q 2019 annual review: references reviewed and updated.	01.19	

References

1. Praluent Prescribing Information. Bridgewater, NJ: Sanofi-Eventis U.S. LLC; November 2018. Available at http://products.sanofi.us/praluent/praluent.pdf. Accessed November 20, 2018.
2. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk. J Am Coll Cardiol. 2016; 68(1): 92-125.
3. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 June 24; 129[suppl 2]: S1-S45.
4. Jacobson TA, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1 – full report. Journal of Clinical Lipidology. March-April 2015; 9(2): 129-169. http://dx.doi.org/10.1016/j.jacl.2015.02.003
5. Goldber AC, Hopkins PN, Toth PP, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. Journal of Clinical Lipidology. June 2011; 5(3S): 1-15.
6. Al-Rasadi K, Al-Waili K, Al-Sabti HA, et al. Criteria for diagnosis of familial hypercholesterolemia: A comprehensive analysis of the different guidelines, appraising their suitability in the Omani Arab population. Oman Medical Journal. 2014; 29(2): 85–91. http://doi.org/10.5001/omj.2014.22
7. Fitchett DH, Hegele RA, Verma S. Statin intolerance. Circulation 2015;131:e389-391. https://doi.org/10.1161/CIRCULATIONAHA.114.013189

8. Food and Drug Administration Center for Drug Evaluation and Research: The Endocrinology and Metabolic Drugs Advisory Committee Meeting Briefing Document BLA 125559 – Praluent (alirocumab) injection. June 9, 2015. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125559Orig1s000ODMemo.pdf. Accessed: May 22, 2018.
9. Lloyd-Jones DM, Morris PB, Minissian MB, et al. 2017 Focused update of the 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk. J Am Coll Cardiol 2017; 70(14):1785-1822. http://dx.doi.org/10.1016/j.jacc.2017.07.745