# Clinical Policy: Alirocumab (Praluent)

Reference Number: CP.PHAR.124
Effective Date: 10.01.15
Last Review Date: 02.22
Line of Business: Commercial, Medicaid

Coding Implications
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 low-density lipoprotein cholesterol (LDL-C)-lowering therapies, in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce LDL-C
- As an adjunct to other LDL-C-lowering therapies in adult patients with homozygous familial hypercholesterolemia (HoFH) to reduce 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.*

It is the policy of health plans affiliated with Centene Corporation® 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 and HoFH. Refer to section I.A.2 below for coverage criteria for HeFH or section I.B below for coverage criteria for HoFH);
      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. Prescribed by or in consultation with a cardiologist, endocrinologist, or lipid specialist;
4. Age ≥ 18 years;
5. 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 <u>two</u> 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 <u>one</u> high and <u>one</u> moderate intensity statins;
         b) A statin risk factor (*see Appendix G*) and history of intolerance to <u>two</u> moderate intensity statins;
6. 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);

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. 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;
9. Treatment plan does not include coadministration with Juxtapid® or Repatha®;
10. Dose does not exceed 75 mg every 2 weeks or 300 mg per month.

**Approval duration:**
**Medicaid –** 3 months
**Commercial –** 6 months or to the member's renewal date, whichever is longer

**B. Homozygous Familial Hypercholesterolemia** (must meet all)**:**
1. Diagnosis of HoFH defined as one of the following (a, b, or c):
   a. Genetic mutation indicating HoFH (e.g., mutations in low density lipoprotein receptor [LDLR] gene, PCSK9 gene, apo B gene, low density lipoprotein receptor adaptor protein 1[LDLRAP1] gene);
   b. Treated LDL-C ≥ 300 mg/dL or non-HDL-C ≥ 330 mg/dL;
   c. Untreated LDL-C ≥ 500 mg/dL, and one of the following (i or ii):
      i. Tendinous or cutaneous xanthoma prior to age 10 years;
      ii. Evidence of HeFH in both parents (e.g., documented history of elevated LDL-C ≥ 190 mg/dL prior to lipid-lowering therapy);
2. Prescribed by or in consultation with a cardiologist, endocrinologist, or lipid specialist;
3. Member meets one of the following (a or b):
   a. Age < 18 years, and LDL-C ≥ 130 mg/dL within the last 60 days despite statin and ezetimibe therapy, unless member has a contraindication (*see Appendix F*) or history of intolerance to each such therapy;
   b. Age ≥ 18 years, and recent (within the last 60 days) LDL-C ≥ 70 mg/dL;
4. For members ≥ 18 years old and 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;

5. For members ≥ 18 years old and 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);
6. If age ≥ 18 years old, 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);
7. Treatment plan does not include coadministration with Juxtapid or Repatha;
8. Dose does not exceed 150 mg every 2 weeks.

**Approval duration:**
**Medicaid –** 3 months
**Commercial –** 6 months or to the member's renewal date, whichever is longer

**C. Other diagnoses/indications**

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial and CP.PMN.53 for Medicaid.

**II. Continued Therapy**

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

1. Currently receiving medication via Centene benefit or member has previously met all 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 every 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 are submitted showing an LDL-C reduction since initiation of the Praluent dose increase.

**Approval duration:**
**Medicaid –** 12 months *(3 months if request is for dose increase)*
**Commercial –** 6 months or to the member's renewal date, whichever is longer

**B. Homozygous Familial Hypercholesterolemia** (must meet all)**:**
1. Currently receiving medication via Centene benefit 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 is responding positively to therapy as evidenced by lab results within the last 3 months showing an LDL-C reduction since initiation of Praluent therapy;
4. If request is for a dose increase, new dose does not exceed 150 mg every 2 weeks.

**Approval duration:**
**Medicaid –** 12 months
**Commercial –** 6 months or to the member's renewal date, whichever is longer

**C. Other diagnoses/indications** (1 or 2)**:**
1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   **Approval duration: Duration of request or 6 months (whichever is less)**; or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial and CP.PMN.53 for Medicaid.

**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 policies – CP.CPA.09 for commercial and CP.PMN.53 for Medicaid or evidence of coverage documents.

## IV. 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
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 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 | |

| FH Criteria | Points | Member's Score† |
|---|---|---|
| **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**<br>***Daily dose shown to lower LDL-C, on average, by approximately ≥ 50%*** |
|---|
| • Atorvastatin 40-80 mg<br>• Rosuvastatin 20-40 mg |
| **Moderate Intensity Statin Therapy**<br>***Daily dose shown to lower LDL-C, on average, by approximately 30% to 50%*** |
| • Atorvastatin 10-20 mg<br>• Fluvastatin XL 80 mg<br>• Fluvastatin 40 mg BID<br>• Lovastatin 40 mg<br>• Pitavastatin 1-4 mg<br>• Pravastatin 40-80 mg<br>• Rosuvastatin 5-10 mg<br>• Simvastatin 20-40 mg |
| **Low Intensity Statin Therapy**<br>***Daily dose shown to lower LDL-C, on average, by < 30%*** |
| • Simvastatin 10 mg<br>• Pravastatin 10-20 mg<br>• Lovastatin 20 mg<br>• Fluvastatin 20-40 mg |

*Appendix F: Statin and Ezetimibe Contraindications*

| **Statins** |
|---|
| • Decompensated liver disease (development of jaundice, ascites, variceal bleeding, encephalopathy)<br>• Laboratory-confirmed acute liver injury or rhabdomyolysis resulting from statin treatment<br>• Pregnancy*, actively trying to become pregnant, or nursing<br>• 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]<br>• Hypersensitivity to ezetimibe (e.g., anaphylaxis, angioedema, rash, urticaria) |

**In July 2021, the FDA requested removal of the contraindication against use of statins in pregnant women. Because the benefits of statins may include prevention of serious or potentially fatal events in a small group of very high-risk pregnant patients, contraindicating these drugs in all pregnant women is not appropriate.*

https://www.fda.gov/safety/medical-product-safety-information/statins-drug-safety-communication-fda-requests-removal-strongest-warning-against-using-cholesterol

*Appendix G: Statin Risk Factors*

| Statin Risk Factors |
|---|
| • Multiple or serious comorbidities, including impaired renal or hepatic function<br>• Unexplained alanine transaminase (ALT) elevations > 3 times upper limit of normal, or active liver disease<br>• Concomitant use of drugs adversely affecting statin metabolism<br>• Age > 75 years, or history of hemorrhagic stroke<br>• 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 | 75 mg SC once every 2 weeks<br>or 300 mg SC once every 4 weeks | 300 mg/month |

| Indication | Dosing Regimen | Maximum Dose |
|---|---|---|
| hypercholesterolemia with ASCVD | 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 | |
| HoFH, HeFH undergoing LDL apheresis | 150 mg SC every 2 weeks | 300 mg/month |

## VI. Product Availability

Single-use pre-filled pen: 75 mg/mL, 150 mg/mL

## VII. References

1. Praluent Prescribing Information. Bridgewater, NJ: Sanofi-Eventis U.S. LLC; April 2021. Available at: http://products.sanofi.us/praluent/praluent.pdf. Accessed October 1, 2021.
2. 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.
3. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018;Nov 10:[Epub ahead of print].
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 October 1, 2021.
9. Manpuya WM, Cho L, Frid D, et al. Treatment strategies in patients with statin intolerance: the Cleveland Clinic experience. American Heart Journal 2013; 166(3):597-603.
10. Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of statins in routine care settings. Ann of Intern Med 2013; 158(7):526-534.

11. Clinical Lipidology Resource Center, sponsored by the National Lipid Association and the Journal of Clinical Lipidology. Genetic classification of dyslipidemia. Available at: http://nlaresourcecenter.lipidjournal.com/Content/PDFs/Tables/1.pdf. Accessed October 1, 2021.
12. Backes JM, Ruisinger JF, Gibson CA, et al. Statin-associated muscle symptoms—managing the highly intolerant. J Clin Lipidol. 2017;11:24-33. Available at: https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2017/05/03/10/43/statin-associated-muscle-symptoms. Accessed October 1, 2021.
13. Thompson PD, Panza G, Zaleski A, et al. Statin-associated side effects. JACC 2016;67(20):2395-2410.
14. Blom DJ, Harada-Shiba M, Rubba P, et al. Efficacy and safety of alirocumab in adults with homozygous familial hypercholesterolemia: The ODYSSEY HoFH trial. J Am Coll Cardiol. 2020; 76(2): 131-142.
15. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline from the American Heart Association/American Stroke Association. Stroke. 2021; 52: e354-e467.

**Coding Implications**

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

| HCPCS Codes | Description |
|---|---|
| J3590 | Unclassified biologics |

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| 3Q 2018 annual review: combined policies for Medicaid and Commercial lines of business; added a separate requirement to check for continued statin use and adherence at reauthorization; Medicaid: 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; Commercial: aligned definition of ASCVD with Medicaid with removal of carotid artery occlusion and renal artery stenosis/stent; lowered minimum LDL value required for initial approval from 100 mg/dL to 70 mg/dL; 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 | 07.23.19 | 08.19 |

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| 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; references reviewed and updated. | | |
| 1Q 2020 annual review: 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; for members on a low intensity statin, modified requirement for statin intolerance to one high and one moderate intensity statins (previously required two of each); modified the requirement for four prior statin trials to two prior statin trials; 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; coding implications added; references reviewed and updated. | 11.02.20 | 02.21 |
| RT4: added criteria for HoFH per updated FDA approved indication and prior clinical guidance. | 04.08.21 | |
| 1Q 2022 annual review: no significant changes; added legacy WellCare line business (WCG.CP.PHAR.124 to be retired) and shortened legacy WCG initial approval duration from 4 to 3 months; removed references to Kynamro since it has been withdrawn from market; references reviewed and updated. | 10.01.21 | 02.22 |

**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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

**Note: For Medicaid members**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.