Clinical Policy: Evolocumab (Repatha)

Reference Number: CP.PHAR.123
Effective Date: 10.15
Last Review Date: 02.19
Line of Business: HIM, Medicaid

Revision Log

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

Description

Evolocumab (Repatha®) is a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor antibody.

FDA Approved Indication(s)

Repatha is indicated:

- To reduce the risk of myocardial infarction, stroke, and coronary revascularization 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 treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) to reduce low-density lipoprotein cholesterol (LDL-C)
- As an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of 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 Repatha 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. 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. 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 D*) regimen for at least the last 4 months due to one of the following (i or ii):
      i. Intolerance to <u>two</u> 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 <u>two</u> high and <u>two</u> moderate intensity statins;
      ii. A statin risk factor (*see Appendix G*) and history of intolerance to <u>two</u> 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 <u>two</u> 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 a history of ezetimibe intolerance (e.g., associated diarrhea or upper respiratory tract infection);
8. Treatment plan does not include coadministration with Juxtapid®, Kynamro®, Praluent®;
9. Dose does not exceed 140 mg every 2 weeks or 420 mg per month.

Approval duration: 3 months

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 30 days despite statin and ezetimibe therapy unless a contraindication (*see Appendix F*) or history of intolerance to each such therapy;
   b. Age ≥ 18 years and recent (within the last 30 days) LDL-C ≥ 70 mg/dL;
4. If age ≥ 18 years old, 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;
5. 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 a history of ezetimibe intolerance (e.g., associated diarrhea or upper respiratory tract infection);
6. Treatment plan does not include coadministration with Juxtapid®, Kynamro®, or Praluent®;
7. Dose does not exceed 420 mg per month.

Approval duration: 3 months

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): HIM.PHAR.21 for health insurance marketplace and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I (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 is responding positively to therapy as evidenced by lab results within the last 3 months showing an LDL-C reduction since initiation of Repatha therapy;
4. If request is for a dose increase, new dose does not exceed either of the following (a or b):
   a. HeFH or ASCVD: Repatha 140 mg every 2 weeks or 420 mg per month;

b. HoFH: Repatha 420 mg per month.

Approval duration: 12 months

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

1. Currently receiving medication via health plan 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): HIM.PHAR.21 for health insurance marketplace 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 – HIM.PHAR.21 for health insurance marketplace 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
LDLRAP1: low density lipoprotein receptor adaptor protein 1
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 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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
rosuvastatin (Crestor®)	5 - 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): hypersensitivity
- Boxed warning(s): none reported

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 score here (0 or 8)
TOTAL SCORE	Definite FH: >8	Place total score 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 10-20mg • 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

High Intensity Statin Therapy ***Daily dose shown to lower LDL-C, on average, by approximately ≥50%***
• 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 another PCSK-9 inhibitor, 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.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
HeFH or hypercholesterolemia with ASCVD	140 mg SQ Q2 weeks or 420 mg SQ once monthly	420 mg/month
HoFH	420 mg SQ once monthly	420 mg/month

VI. Product Availability

- Prefilled syringe and SureClick autoinjector: 140 mg/mL
- Prefilled cartridge Pushtronex system (on-body infusor): 420 mg/3.5 mL

VII. References

1. Repatha Prescribing Information. Thousand Oaks, CA: Amgen, Inc.; October 2018. Available at: http://pi.amgen.com/united_states/repatha/repatha_pi_hcp_english.pdf. Accessed November 20, 2018.
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. 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. 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

Reviews, Revisions, and Approvals	Date	Approval Date
Policy created	09.15	10.15
Converted policy to new template. HoFH criteria: Signs changed from ">" to "≥" for following criteria: Treated LDL-C ≥ *300 mg/dL* or *non-HDL-C ≥ 330 mg/dL*; *Untreated LDL-C ≥ 500 mg/dL*, and one of the following (i or ii): Evidence of HeFH in both parents (e.g., documented history of elevated *LDL-C ≥ 190 mg/dL* prior to lipid-lowering therapy); Added "statin intolerance" criteria statement for HoFH members < 18 years of age under requirement for statin therapy; Added examples of Zetia intolerance; Added Repatha dosage for ASCVD, HeFH, and HoFH per PI. Incorpoated ASCVD, HoFH, TLC appendices into the criteria. Combined Zetia and statin contraindications (App D) and added nursing as a contraindication. Added scoring instructions to the Dutch criteria appendix. Statin risk factors are listed at App E. Modified renewal duration to 12 months. Added requirement for the use of statin and zetia therapy for the last 4 months to ensure that LDL-C submitted reflect the full effect of statin/zetia use after a full 12 weeks of therapy	10.16	10.16
Policy converted to new template. Safety criteria was applied according to the safety guidance discussed at CPAC and endorsed by Centene Medical Affairs. References updated.	09.17	10.17
Modified definition of ASCVD to include nonhemorrhagic stroke or transient ischemic attack.	11.17	
No clinical changes Added new indication to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease to the FDA approved indication section.	12.14.17	
3Q 2018 annual review: combined policies for Medicaid, HIM, and Commercial lines of business; Medicaid/HIM: removed requirement against hypersensitivity; removed requirement for therapeutic lifestyle changes; aligned definition of ASCVD with commercial by addition of acute coronary syndrome and clinically significant CHD; aligned trial of Zetia language by requiring concomitant statin; added hydrophilic statin with intermittent dosing requirement; added diagnosis of HeFH via Simon Broome criteria as alternative option to WHO criteria; 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; Medicaid/Commercial: added that lab results must be within the last 3 months for continued therapy; references reviewed and updated.	05.22.18	08.18
Removed Commercial line of business (refer to CP.CPA.269)	10.23.18	
1Q 2019 annual review: no significant changes; references reviewed and updated.	11.20.18	02.19

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.

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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.

For Health Insurance Marketplace members, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the non-formulary policy; HIM.PA.103.