Clinical Policy: Evolocumab (Repatha)

Reference Number: IN.CP.PHAR.123
Effective Date: 10.01.15
Last Review Date: 12.21
Line of Business: Medicaid

Coding Implications
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 [HeFH]) 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. Must meet all of the following:

1. Diagnosis of one of the following (a or b):
    a. Diagnosis of hyperlipidemia or cardiovascular disease with a baseline LDL-C >=70 mg/dL
    b. Diagnosis of homozygous familial hypercholesterolemia (HoFH) with a baseline LDL-C >=70 mg/dL
2. Prescribed by or in consultation with a cardiologist, endocrinologist, or lipid specialist;
3. Age ≥ 18 years (HoFH – member must be 13 years or older)
4. For members on statin therapy, one of the following (a , b, c or d):
    a. Previous trial of high intensity statin therapy (atorvastatin 40mg/80mg or rosuvastatin 20mg/40mg) for 90 of the past 120 days
    b. Intolerance of at least two statins, including one high-intensity statin
    c. Medical rationale against use of statin therapy

d. Concurrent use of at least one additional lipid-lowering therapy (HoFH only)

5. Dose does not exceed 140 mg every 2 weeks
6. Does does not exceed 420 mg every two weeks or once a month. (HoFH is doses at 420mg only)

Approval duration: 12 months

B. 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.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**

1. History of Repatha (evolocumab) within the past 90 days
2. One of the following:
   a. Continued use of high intensity statin therapy (atorvastatin 40mg/80mg or rosuvastatin 20mg/40mg) for 90 of the past 120 days
   b. Documented intolerance to statin therapy
   c. Medical rationale against use of statin therapy
   d. Continued concurrent use of at least one additional lipid-lowering therapy (HoFH only)
3. Reduction in LDL-C from baseline
4. One of the following:
   a. Dose requested is 140mg every 2 weeks
   b. Dose requested is 420mg every two weeks or once monthly (HoFH is dosed at 420mg only)

Approval duration: 12 months

B. Other diagnoses/indications:

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.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.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
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 - 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
Patient with premature* cerebral or peripheral vascular disease	1	

FH Criteria	Points	Member's Score†
		(0, 1 or 2)
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 10-20 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 • 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

Statin Risk Factors
• 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.
- 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	140 mg SC Q2 weeks or 420 mg SC once monthly	420 mg/month
HoFH	420 mg SC once monthly; Dosage can be increased to 420 mg every 2 weeks if a clinically meaningful response is not achieved in 12 weeks	420 mg/2 weeks

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

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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.
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in-cardiology/ten-points-to-remember/2017/05/03/10/43/statin-associated-muscle-symptoms. Accessed June 10, 2019.
13. Thompson PD, Panza G, Zaleski A, et al. Statin-associated side effects. JACC 2016;67(20):2395-2410.

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
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
Policy updated to include coverage criteria for primary hyperlipidemia (including but not limited to HeFH); concomitant statin usage section	07.23.19	08.19

Reviews, Revisions, and Approvals	Date	P&T Approval Date
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: For primary hyperlipidemia/ASCVD (I.A.)—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; For HoFH (I.B.)—increased the timeframe for LDL-C lab draws from 30 days to 60 days; 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 two statins with documentation of statin risk factors or intolerance; criteria for statin-rechallenge in the setting of SAMS are added; Appendix E updated based on 2018 ACC/AHA guidelines; references reviewed and updated.	11.05.19	02.20
1Q 2021 annual review: no significant changes; reference to HIM.PHAR.21 revised to HIM.PA.154; added coding implications; references reviewed and updated.	11.02.20	02.21
Per March SDC, removed HIM line of business.	03.26.21	05.21
RT4: Updated HoFH continuation criteria based on FDA label update to allow a maximum dose of 420 mg every 2 wks if clinically meaningful response not achieved after 12 wks of 420 mg monthly.	06.29.21	
Updated per IN Medicaid State Moratorium	12.21	10.21

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. 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.