Clinical Policy Title:	evolocumab
Policy Number:	RxA.264
Drug(s) Applied:	Repatha®
Original Policy Date:	02/07/2020
Last Review Date:	06/10/2021
Line of Business Policy Applies to:	All lines of business

Background

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

- In adults with established cardiovascular disease (CVD) to reduce the risk of myocardial infarction, stroke, and coronary revascularization.
- 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 patients with homozygous familial hypercholesterolemia (HoFH), to reduce LDL-C.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
evolocumab (Repatha®)	Primary hyperlipidemia (including HeFH) or cardiovascular disease	Initial recommended dosage is 140 mg every 2 weeks or 420 mg once monthly administered subcutaneously. If switching dosage regimens, administer the first dose of the new regimen on the next scheduled date of the prior regimen. The 420 mg dose of evolocumab can be administered over 5 minutes by using the single-use on-body infusor with prefilled cartridge, or by giving 3 injections consecutively within 30 minutes using the single-use prefilled autoinjector or single-use prefilled syringe.	420 mg/month
	HoFH	The initial recommended dosage is 420 mg once monthly administered subcutaneously. The dosage can be increased to 420 mg every 2 weeks if a clinically meaningful response is not achieved in 12 weeks. Patients on lipid apheresis may initiate treatment with 420 mg every 2 weeks to correspond with their apheresis schedule. Administer evolocumab after the apheresis session is complete.	420 mg/month

Dosage Forms

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

- Injection: 140 mg/mL solution in a single-use prefilled syringe

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

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)
      i. Documentation of one of the following (a or b):
         a) Presence of a genetically mediated form of primary hyperlipidemia as evidence by confirmatory genetic testing results;
         b) A diagnosis of secondary hyperlipidemia has been ruled out with documentation of 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 which can increase 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 or greater for genetically mediated primary hyperlipidemias;
         b) 220 mg/dL or greater for non-genetically mediated primary hyperlipidemias;
   b. Atherosclerotic cardiovascular disease (ASCVD) as evidenced by a history of any of any one of the following conditions (i-vii):
      i. Acute coronary syndromes;
      ii. Clinically significant coronary heart disease (CHD) diagnosed by invasive or non-invasive 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 or greater;
   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 greater than 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. Member is 18 years of age or older;
5. For members on statin therapy, both of the following (a and b):
   a. Evolocumab is prescribed in conjunction with a statin at the maximally tolerated dose;
   b. Member has been adherent for at least the last for (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 two high and two moderate intensity statins;
         b) A statin risk factor (*see Appendix G*) and history of intolerance to two 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 four (4) statins, two (2) of which must be hydrophilic statins (i.e., 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 30 days) LDL-C of one of the following (a, b, or c):
   a. 70 mg/dL or greater for ASCVD;
   b. 100 mg/dL or greater for genetically mediated severe primary hyperlipidemia (including HeFH);
   c. 130 mg/dL or greater for non-genetically mediated severe primary hypercholesterolemia;
9. Treatment plan does not include coadministration with Juxtapid®, Kynamro®, Praluent®;
10. Dose does not exceed 140 mg every 2 weeks or 420 mg per month.

Approval Duration
Commercial: 6 months
Medicaid: 6 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 greater or non-HDL-C 330 mg/dL or greater;
   c. Untreated LDL-C 500 mg/dL or greater, 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 or greater 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. Member is less than 18 years of age and has an LDL-C of 130 mg/dL or greater within the last 30 days despite statin and ezetimibe therapy unless contraindication (*see Appendix F*) or history of intolerance to each such therapy;
   b. Member is 18 years of age or older and recent (within the last 30 days) LDL-C that is 70 mg/dL or higher;
4. If member is 18 years of age or older, member has been adherent to a high intensity statin (*see Appendix E*) regimen for at least the last four (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 four (4) months due to one of the following (i or ii):
      i. Intolerance to two (2) high intensity statins;
      ii. A statin risk factor (*see Appendix G);* and history of intolerance to two (2) moderate intensity statins;
   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 (2) high and two (2) moderate intensity statins;
      ii. A statin risk factor (*see Appendix G*) and history of intolerance to two (2) moderate intensity statins;
5. If member is 18 years of age or older, member has been adherent to ezetimibe therapy for at least the last four (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
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. All Indications in Section I (must meet all):
1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
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 12 months showing an LDL-C reduction since initiation of therapy;
4. If request is for a dose increase, new dose does not exceed either of the following (a or b):
   a. Primary hyperlipidemia (including HeFH) or ASCVD: 140 mg every 2 weeks or 420 mg per month;
   b. HoFH: 420 mg per month.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

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
SC: Subcutaneously
TIA: Transient ischemic attack
WHO: World Health Organization

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
ezetimibe/ simvastatin (Vytorin®)	10/40 mg PO once daily	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 once daily	10 mg/day
atorvastatin (Lipitor®)	40 mg PO once daily	80 mg/day
rosuvastatin (Crestor®)	5 - 40 mg PO once daily	40 mg/day
Praluent® (alirocumab)	HeFH and ASCVD 75mg SC once every 2 weeks or 300 mg SC once every 4 weeks. If response to 75 mg every 2 weeks or 300 mg every 4 weeks is inadequate, dose may be increased to 150 mg once every 2 weeks.	300 mg/month

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 a serious hypersensitivity reaction to evolocumab.

- Boxed Warning(s):
  - None reported.

APPENDIX D: General Information

- 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):
     i. 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

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

ii. 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):

Tendinous xanthomas in patient or relative (parent, child, sibling, grandparent, aunt, uncle)

i. 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

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

APPENDIX F: Statin and Ezetimibe Contraindications

Statin
• 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 greater than 75 years of age, 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:
  a. Familial hypercholesterolemia
  b. Familial combined hyperlipidemia (FCHL)
  c. Polygenic hypercholesterolemia
  d. 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 re-challenge 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.

References

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Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy was reviewed: 1. Clinical Policy Title was updated. 2. Drug(s) Applied was updated. 3. Line of Business Policy Applies to was update to all lines of business. 4. Continued Therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance..." 5. Initial Approval criteria: Commercial and Medicaid approval duration were updated from member's renewal date to 6 months. 6. Trial/failure of Praluent criteria was removed from initial approval criteria. 7. Continued Approval criteria II.A.3 “lab results within the past 3 months” was updated to “lab results within the past 12 months”. 8. Continued Approval criteria: Commercial and Medicaid approval duration were updated from member's renewal date to 6 months. 9. Updated APPENDIX F: Statin and Ezetimibe Contraindications 10. References were updated. 11. Updated Dosing Information to include administration details for single-use prefilled autoinjector or single-use prefilled syringe. 12. Updated dosage form to include Injection: 140 mg/mL solution in a single-use prefilled syringe. 13. Updated Dosing Regimen to include: The 420 mg dose of REPATHA can be administered over 9 minutes by using the single-use on-body infusor with prefilled cartridge, or by giving 3 injections consecutively within 30 minutes using the single-use prefilled autoinjector or single-use prefilled syringe. 14. Updated Appendix B Therapeutic Alternatives – included “once daily” for dosing regimen for Vytorin®, Zetia®, Lipitor®, Crestor®.	07/16/2020	09/14/2020

Policy was reviewed: 1. Background was updated. 2. Dosing Information was updated. 3. Clinical policy - Verbiage added: ‘‘The provision of provider samples does not guarantee coverage under the provisions of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage” after “Provider must submit…” 4. Initial approval criteria 1.A.1.a verbiage was updated. 5. Continued Therapy criteria II.A.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance..." and length of approval updated. 6. References were reviewed and updated.	04/08/2021	06/10/2021