Clinical Policy: Evolocumab (Repatha)
Reference Number: ERX.SPA.169
Effective Date: 01.11.17
Last Review Date: 11.17

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 as an adjunct to diet and:
• Maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C)
• Other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C

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

Policy/Criteria
Provider must submit documentation (which may include office chart notes and lab results) supporting that member has met all approval criteria

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ 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 defined as 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 B);
            ii. Definite diagnosis per Simon Broome criteria (see Appendix B);
         b. ASCVD as evidenced by a history of any of the following conditions (i, ii, iii, iv, v, vi, or vii):
            i. Myocardial infarction;
            ii. Stable or unstable angina;
            iii. Coronary or other arterial revascularization;
            iv. Peripheral arterial disease presumed to be of atherosclerotic origin;
            v. Acute coronary syndromes;
            vi. Stroke or transient ischemic attack (TIA);
            vii. 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);
      2. Prescribed by or in consultation with a cardiologist, endocrinologist, or lipid specialist;
      3. Age ≥ 18 years;
      4. Recent (within the last 30 days) low-density lipoprotein cholesterol (LDL-C) ≥ 100 mg/dL;
      5. Member has received a high intensity statin (see Appendix C) adherently for at least the last 4 months, unless one of the following applies (a, b, or c):
         a. Statin therapy is contraindicated per Appendix D;
         b. Member has received a moderate intensity statin (see Appendix C) adherently for at least the last 4 months due to (i or ii):
i. Intolerance to two high intensity statins;
ii. A statin risk factor (see Appendix E);

c. Member is unable to take a high or moderate intensity statin due to (i or ii):
   i. Intolerance to two high and two moderate intensity statins;
   ii. A statin risk factor (see Appendix E) and history of intolerance to two moderate intensity statins;

6. Meets one of the following (a or b):
   a. Use is in conjunction with maximally tolerated statin;
   b. If member is statin intolerant, member has tried at least 2 of the hydrophilic statins (i.e., pravastatin, fluvastatin, or rosuvastatin) titrated from lowest possible dose;

7. Member has received Zetia therapy adherently for at least the last 4 months, unless contraindicated per Appendix D or member has a history of Zetia intolerance (e.g., associated diarrhea or upper respiratory tract infection);

6. Dose does not exceed 140 mg every 2 weeks or 420 mg once monthly.

Approval duration: 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 (LDLR, PCSK9, apoB, LDLRAP1);
      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 Zetia therapy unless there is a contraindication (see Appendix D) or history of intolerance to each such therapy;
      b. Age ≥ 18 years and recent (within the last 30 days) LDL-C ≥ 100 mg/dL;
   4. If member is ≥ 18 years, has received a high intensity statin (see Appendix C) adherently for at least the last 4 months, unless one of the following applies (a, b, or c):
      a. Statin therapy is contraindicated per Appendix D;
      b. Member has received a moderate intensity statin (see Appendix C) adherently for at least the last 4 months due to (i or ii):
         i. Intolerance to two high intensity statins;
         ii. A statin risk factor (see Appendix E);
      c. Member is unable to take a high or moderate intensity statin due to (i or ii):
         i. Intolerance to two high and two moderate intensity statins;
         ii. A statin risk factor (see Appendix E) and history of intolerance to two moderate intensity statins;
   5. If member is ≥ 18 years, has received Zetia therapy adherently for at least the last 4 months, unless contraindicated per Appendix D or member has a history of Zetia intolerance (e.g., associated diarrhea or upper respiratory tract infection);
   6. Dose does not exceed 420 mg once monthly.

Approval duration: 6 months

C. Other diagnoses/indications
   1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy
   A. All Indications in Section I (must meet all):
      1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
      2. If statin tolerant, documentation of adherence to maximally tolerated statin therapy;
3. Lab results within the last 3 months are submitted showing an LDL-C reduction (defined as at least 25% LDL reduction from baseline, LDL < 70 mg/dL for high risk patients, or LDL < 100 mg/dL for medium risk patients) since initiation of Repatha therapy (see Appendix B);

4. If request is for a dose increase, new dose does not exceed (a or b):
   a. HeFH or ASCVD: 140 mg every 2 weeks or 420 mg once monthly;
   b. HoFH: 420 mg once monthly.

**Approval duration: 12 months**

B. Other diagnoses/indications (must meet 1 or 2):
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   **Approval duration: Duration of request or 6 months (whichever is less);** or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 policy – ERX.PA.01 or evidence of coverage documents;
   B. Coadministration with Juxtapid (lomitapid), Kynamro (mipomersen), or Praluent (alirocumab).

IV. Appendices/General Information

**Appendix A: Abbreviation/Acronym Key**
- ACC/AHA: American College of Cardiology/American Heart Association
- ALT: alanine transaminase
- apoB: apolipoprotein B
- ASCVD: atherosclerotic cardiovascular disease
- CVD: cardiovascular disease
- FDA: Food and Drug Administration
- FH: familial hypercholesterolemia
- HeFH: heterozygous familial
- HoFH: homozygous familial
- LDLR: low density lipoprotein receptor
- LDL-C: low density lipoprotein cholesterol
- PCSK9: proprotein convertase subtilisin kexin 9

**Appendix B: General Information**
- Dutch Lipid Clinic Network criteria for Familial Hypercholesterolemia (FH)

<table>
<thead>
<tr>
<th>FH Criteria</th>
<th>Points</th>
<th>Member’s Score†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family History</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-degree relative with known premature* coronary and vascular disease</td>
<td>1</td>
<td>Place highest score here (0, 1 or 2)</td>
</tr>
<tr>
<td>First-degree relative with known LDL-C level above the 95th percentile</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>First-degree relative with tendinous xanthomata and/or arcus cornealis</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Children aged &lt; 18 years with LDL-C level above the 95th percentile</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical History</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient with premature* coronary artery disease</td>
<td>2</td>
<td>Place highest score here (0, 1 or 2)</td>
</tr>
<tr>
<td>Patient with premature* cerebral or peripheral vascular disease</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Physical Examination</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tendinous xanthomata</td>
<td>6</td>
<td>Place highest score here (0, 4 or 6)</td>
</tr>
<tr>
<td>Arcus cornealis prior to age 45 years</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><strong>Cholesterol Levels - mg/dL (mmol/liter)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C ≥330 mg/dL (≥8.5)</td>
<td>8</td>
<td>Place highest score here</td>
</tr>
<tr>
<td>LDL-C 250 – 329 mg/dL (6.5 – 8.4)</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>
## FH Criteria

<table>
<thead>
<tr>
<th>FH Criteria</th>
<th>Points</th>
<th>Member’s Score†</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C 190 – 249 mg/dL (5.0 – 6.4)</td>
<td>3</td>
<td>(0, 1, 3, 5 or 8)</td>
</tr>
<tr>
<td>LDL-C 155 – 189 mg/dL (4.0 – 4.9)</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

### DNA Analysis

<table>
<thead>
<tr>
<th>DNA Analysis</th>
<th>Points</th>
<th>Member’s Score†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional mutation in the LDLR, apo B or PCSK9 gene</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

**TOTAL SCORE**

<table>
<thead>
<tr>
<th>Definite FH: &gt;8</th>
<th>Place score total here __</th>
</tr>
</thead>
</table>

*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. Tendon 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
  - 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
- In July 2017, the FDA announced that Repatha was granted priority review for Amgen’s supplemental Biologics License Application to update the prescribing information to include risk reduction of major cardiovascular events based on data from the FOURIER study. The approval for this update is still pending with a Prescription Drug User Fee Act date of December 2, 2017.

### Appendix C: 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
    - Fluvastatin 20–40 mg
    - Pravastatin 10–20 mg
    - Pitavastatin 1 mg
    - Lovastatin 20 mg
Appendix D: Statin and Zetia 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;

- **Zetia**
  - Moderate or severe hepatic impairment (Child-Pugh classes B and C);
  - Hypersensitivity to Zetia (e.g., anaphylaxis, angioedema, rash, urticaria).

Appendix E: Statin Risk Factors

- Multiple or serious comorbidities, including impaired renal or hepatic function;
- Unexplained alanine aminotransferase elevations > 3 times the 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 F: Therapeutic Alternatives

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vytorin® (ezetimibe/simvastatin)</td>
<td>10/40 mg PO QD</td>
<td>10/40 mg PO QD (use of the 10/80 mg dose is restricted to patients who have been taking simvastatin 80 mg for ≥ 12 months without evidence of muscle toxicity)</td>
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<tr>
<td>atorvastatin (Lipitor®)</td>
<td>40 mg PO QD</td>
<td>80 mg PO QD</td>
</tr>
<tr>
<td>rosuvastatin (Crestor®)</td>
<td>5 - 40 mg PO QD</td>
<td>40 mg PO QD</td>
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</table>

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.

V. Dosage and Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>HeFH or ASCVD</td>
<td>140 mg SC Q2 weeks or 420 mg SC once monthly</td>
<td>420 mg once monthly</td>
</tr>
<tr>
<td>HoFH</td>
<td>420 mg SC once monthly</td>
<td>420 mg once monthly</td>
</tr>
</tbody>
</table>

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

Evolocumab


<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy created</td>
<td>11.16</td>
<td>12.16</td>
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<tr>
<td>4Q17 Annual Review</td>
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<tr>
<td>- Converted to new template</td>
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<tr>
<td>- Added clinically significant coronary heart disease (CHD) diagnosed by invasive or noninvasive testing as documentation of ASCVD</td>
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<tr>
<td>- Changed LDL level from ≥ 70 mg/dL to ≥ 100 mg/dL</td>
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<tr>
<td>- Added Simon Broome criteria for diagnosis of HeFH</td>
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<tr>
<td>- Added requirement of trial of at least 2 of the hydrophilic statins associated with less ADEs (pravastatin, fluvastatin, or rosuvastatin)</td>
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<tr>
<td>- Increased initial approval duration from 3 to 6 months to allow for buffer (member picking up med, learning how to self-inject, and going back to MD for re-evaluation)</td>
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<tr>
<td>- Added use in conjunction with max tolerated statin</td>
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<tr>
<td>- Coadministration with Juxtapid (lomitapid), Kynamro (mipomersen), or Repatha (evolocumab) moved to section III from section I</td>
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<tr>
<td>- Removed therapeutic life style changes since it’s not objectively measured</td>
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<tr>
<td>- Specified LDL-C reduction required at re-authorization</td>
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<tr>
<td>- Added requirement of adherence to statin for statin tolerant patients</td>
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<tr>
<td>Important Reminder</td>
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</tbody>
</table>
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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.

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