### Repatha

#### Description

Repatha (evolocumab)

#### Background

Repatha is used in addition to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia (HeFH), homozygous familial hypercholesterolemia (HoFH) or patients with clinical atherosclerotic cardiovascular disease such as heart attacks or strokes, who require additional lowering of LDL cholesterol. HeFH is an inherited condition that causes high levels of low-density lipoprotein (LDL) cholesterol. Repatha provides another treatment option for patients with known cardiovascular disease who have not been able to lower their LDL cholesterol enough on statins. (1).

Repatha is an antibody that targets a specific protein, called PCSK9, which works by reducing the number of receptors on the liver that remove LDL cholesterol from the blood. By blocking PCSK9's ability to work, more receptors are available to rid LDL cholesterol from the blood and, as a result, lower LDL cholesterol levels (1).

#### Regulatory Status

FDA Indicated for: Repatha is a PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) inhibitor antibody indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of:

1. Maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who requires additional lowering of low density lipoprotein cholesterol (LDL-C).
2. Other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

**Limitations of Use:**
The effect of Repatha on cardiovascular morbidity and mortality has not been determined (1).

The safety and effectiveness of Repatha have not been established in pediatric patients with HoFH who are younger than 13 years old. The safety and effectiveness of Repatha have not been established in pediatric patients with primary hyperlipidemia or HeFH (1).

Physicians often measure CK in patients about to begin statins or already on statins. Many physicians will not start or continue statins to lower LDL-C in asymptomatic patients with high CK because of concern about possible statin-induced myositis-rhabdomyolysis. High pretreatment CK, predominantly 1 to 5 times the UNL, as in the current report, should not be an impediment to start or continue statins to lower LDLC (5).

**Spectrum of statin-associated muscle adverse events:** (6)

1. **Myalgia**—unexplained muscle discomfort often described as “flu-like” symptoms with normal CK level. The spectrum of myalgia complaints includes:
   - Muscle aches
   - Muscle soreness
   - Muscle stiffness
   - Muscle tenderness
   - Muscle cramps with or shortly after exercise (not nocturnal cramping).
2. **Myopathy**—muscle weakness (not attributed to pain and not necessarily associated with elevated CK)
3. **Myositis**—muscle inflammation
4. **Myonecrosis**—muscle enzyme elevations or hyperCKemia
   - Mild > 3-fold greater than baseline untreated CK levels or normative upper limit that are adjusted for age, race, and sex
   - Moderate ≥ 10-fold greater than untreated baseline CK levels or normative upper limit that are adjusted for age, race, and sex
   - Severe ≥ 50-fold above baseline CK levels or normative upper limit that are adjusted for age, race, and sex
5. **Myonecrosis with myoglobinuria or acute renal failure** (increase in serum creatinine ≥ 0.5 mg/dL (clinical rhabdomyolysis)
Statin intolerance is widely defined as not being able to tolerate a registered statin dose, due to side effects such as myalgia-myopathy, myositis, or elevation of serum liver enzyme activities. Statin intolerance has been also described as a clinical syndrome with the following characteristics: (7)

1. The inability to tolerate at least 2 different statins – one statin at the lowest starting average daily dose and the other statin at any dose
2. Intolerance associated with confirmed, intolerable statin-related adverse effect(s) or significant biomarker abnormalities
3. Symptom or biomarker changes resolution or significant improvement upon dose decrease or discontinuation
4. Symptoms or biomarker changes not attributable to established predispositions such as drug-drug interactions and recognized conditions increasing the risk of statin intolerance

The ACC Statin Intolerance App guides clinicians through the process of managing and treating patients who report muscle symptoms while on statin therapy. The App is available for free online at Tools.ACC.org/StatinIntolerance or for download in the App stores. Search “ACC Statin Intolerance.”

Related policies
Juxtapid, Praluent

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Repatha may be considered medically necessary in patients 13 years of age or older for the treatment of homozygous familial hypercholesterolemia (HoFH), Repatha may be considered medically necessary in patients 18 years of age or older heterozygous familial hypercholesterolemia (HeFH) or for patients that have atherosclerotic cardiovascular disease if the conditions indicated below are met.

Repatha is considered investigational in patients for all other ages and for all other indications.

Prior-Approval Requirements

Diagnoses
Patient must have **ONE** of the following:

1. **Homozygous familial hypercholesterolemia (HoFH)**

   AND **ALL** of the following:
   a. 13 years and older
   b. Provided documentation (medical records, patient’s chart) of confirmed diagnosis by LDL-R DNA Sequencing Test or APOB (hypercholesterolemia) Mutation Analysis
   c. Genetic confirmation of two mutant alleles at the LDLR, Apo-B, PCSK9, ARH adaptor protein 1/LDLRAP1 gene locus
   d. Provided documentation (medical records, laboratory reports) of baseline and/or current LDL-C level ≥ 100 mg/dL in the past 90 days

2. **Heterozygous familial hypercholesterolemia (HeFH)**
   a. 18 years and older
   b. Provided documentation (medical records, laboratory reports) of baseline and/or current LDL-C level ≥ 100 mg/dL in the past 90 days

   AND **ONE** of the following:
   i. Provided documentation (medical records, patient’s chart) of confirmed diagnosis by LDL-R DNA Sequencing Test or APOB (hypercholesterolemia) Mutation Analysis
   ii. Dutch Lipid Clinic Network Criteria score > 5
   iii. Simon-Broome Diagnostic Criteria for definite familial hypercholesterolemia

3. **Atherosclerotic cardiovascular disease (ASCVD)**
   a. 18 years and older
   b. Laboratory report or medical records of LDL-C 70 mg/dL or greater in the past 90 days

   AND **ONE** of the following for ASCVD:
   a. Documented history of **ONE** of the following atherosclerotic cardiovascular disease (ASCVD) or cardiovascular events:
      i. Acute coronary syndrome
      ii. Myocardial infarction
      iii. Stable or unstable angina
      iv. Coronary or other arterial revascularization procedure (such as PTCA, CABG)
v. Transient ischemic attack (TIA)
vi. Peripheral arterial disease presumed to be of atherosclerotic origin
vii. Findings from CT angiogram or catheterization consistent with clinical ASCVD

b. At high risk for atherosclerotic cardiovascular disease (ASCVD) or cardiovascular event based on 10-year risk score used by ONE of the following tools:
   i. ASCVD Pooled Cohort Risk Assessment—score greater than or equal to 7.5%
   ii. Framingham Risk Score—score greater than or equal to 20%

AND ALL of the following for ALL diagnoses:
   1. Patient will be assessed for response (ie., LDL-C reduction) and adherence to the prescribed lipid lowering regiment after 3 months
   2. NO dual therapy with another proprotein convertase subtilisin/kexin type 9 inhibitor or Juxtapid

AND ONE of the following for ALL diagnoses:
   1. Inadequate response to 3 months of prior therapy with at least ONE trial of a high intensity statin in combination with Zetia (ezetimibe)
   2. Intolerance to a statin
      a. Provide medical records of documentation of the following intolerable adverse reactions with ONE of the following:
         i. Intolerable and persistent (ie: more than 2 weeks) muscle symptoms (eg., muscle pain, weakness, cramps) with ONE of the following:
            1) Myalgia (muscle symptoms without CK elevations) – Patient has undergone prior therapy with at least TWO trials of different statins with or without Zetia (ezetimibe) with a documented reappearance of the muscle symptoms
            2) Myositis (muscle symptoms with CK elevations) – Documentation provided indicated creatinine kinase (CK) levels greater than 3 times upper normal limit and/or rhabdomyolysis with CK levels greater than 2,500 IU/L
      b. Intolerable and persistent hepatotoxicity after TWO trials of different statins with or without Zetia (ezetimibe) with ALL of the following:
         i. Documentation indicating persistent elevations (>3 times the upper limit of normal occurring on 2 more occasions) of serum transaminases or the presence of jaundice
ii. Secondary causes of elevations in hepatic transaminase levels have been ruled out (eg., infection, medications, herbal supplements)

3. Contraindication to a statin must have ONE of the following:
   a. Currently pregnant or may become pregnant
   b. Nursing mother

All approved requests are subject to review by a clinical specialist for final validation and coverage determination once all required documentation has been received. Current utilization, including samples, does not guarantee approval of coverage.

Prior – Approval Renewal Requirements

Diagnoses

Patient must have ONE of the following:

1. Heterozygous familial hypercholesterolemia (HeFH)
2. Homozygous familial hypercholesterolemia (HoFH)
3. Atherosclerotic cardiovascular disease (ASCVD)

AND ALL of the following:
   a. Documentation has been provided indicating the reduction in LDL-C (i.e., chart notes, medical record, and/or laboratory reports) of ONE of the following:
      i. Percentage reduction of LDL-C level is greater than or equal to (≥) 40%, compared to the level immediately prior to starting a PCSK9 inhibitor
      ii. Absolute LDL-C is less than (<) 100mg/dL
   b. Patient will be assessed for adherence to the prescribed lipid lowering regimen
   c. NO dual therapy with another proprotein convertase subtilisin/kexin type 9 inhibitor or Juxtapid

All approved requests are subject to review by a clinical specialist for final validation and coverage determination once all required documentation has been received. Current utilization, including samples, does not guarantee approval of coverage.
Section: Prescription Drugs  Effective Date: July 1, 2019
Subsection: Cardiovascular Agents  Original Policy Date: September 9, 2015
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<tr>
<td>Atorvastatin (Lipitor) 40 - 80 mg a day</td>
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<td>Simvastatin (Zocor) 10mg a day</td>
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<tr>
<td>Rosuvastatin (Crestor) 20 - 40mg a day</td>
<td>Rosuvastatin (Crestor) 5 - 10mg a day</td>
<td>Pravastatin (Pravachol) 10 - 20mg a day</td>
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<tr>
<td>Simvastatin (Zocor) 80 mg a day</td>
<td>Simvastatin (Zocor) 20 - 40mg a day</td>
<td>Lovastatin (Mevacor) 20mg a day</td>
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Policy Guidelines

Pre - PA Allowance
None

Prior - Approval Limits

Quantity
- Repatha 140mg 9 syringes per 90 days OR 3 syringes per 90 days
- 420mg

Duration 12 months

Prior – Approval Renewal Limits

Quantity
- Repatha 140mg 9 syringes per 90 days OR 3 syringes per 90 days
- 420mg

Duration 12 months
Rationale

Summary
Repatha is used in addition to diet and maximally tolerated statin therapy in patients with homozygous familial hypercholesterolemia (HoFH), heterozygous familial hypercholesterolemia (HeFH) or patients with clinical atherosclerotic cardiovascular disease such as heart attacks or strokes, who require additional lowering of LDL cholesterol. Repatha is an antibody that targets a specific protein, called PCSK9, which works by reducing the number of receptors on the liver that remove LDL cholesterol from the blood. By blocking PCSK9’s ability to work, more receptors are available to get rid of LDL cholesterol from the blood and, as a result, lower LDL cholesterol levels. The safety and efficacy of Repatha in pediatric patients 18 years or less have not been established (1-6).

Prior approval is required to ensure the safe, clinically appropriate and cost effective use of Repatha while maintaining optimal therapeutic outcomes.

References
September 2015  
Addition to PA  
Annual review and change of active liver disease from the contraindications to intolerance section.  
Addition of "Current utilization, including samples, does not guarantee approval of coverage," to the criteria

December 2015  
Annual review

July 2016  
Addition of 420mg syringe and documentation in the past 60 days for LDL levels  
Policy number change from 5.16.08 to 5.40.08

September 2016  
Annual editorial review and reference update  
Change in intolerable and persistent (ie: more than 2 weeks) muscle symptoms (eg., muscle pain, weakness, cramps) with ALL of the following-  
Change from documentation provided indicated creatinine kinase (CK) levels greater than 10 times upper normal limit and/or rhabdomyolysis with CK levels greater than 10,000 IU/L – to 5 times and 2,500 IU/L

December 2016  
Annual review

September 2017  
Annual editorial review and reference update  
Removal of the following requirements: prescribed or recommended by cardiologist, endocrinologist, or lipidologist  
Change to the requirement for intolerable and persistent muscle symptoms and hepatotoxicity from “one high intensity statin and one low or moderate intensity statin with Zetia” to “two trials of different statins with or without Zetia”.  
Change of ASCVD LDL level from 100 to 70.  
Change of ASCVD Pooled Cohort Risk Assessment from 15% to 7.5%, change in intolerance to a statin caused by muscle symptoms the requirement of combination of Zetia and change in CK levels from 5 times ULN to 3 times ULN per SME

December 2017  
Annual editorial review

July 2018  
Change of HeFH Dutch Lipid clinical network score from ≥8 to >5, change of initiation LDL levels from past 60 days to past 90 days, change in initiation approval length from 3 months to 12 months, addition of inadequate response, intolerance, contraindication to statins to all diagnoses for initiation

August 2018  
Redefined inadequate response to statins

September 2018  
Annual review

November 2018  
Annual editorial review and reference update. Removal of Kynamro from dual therapy questions

May 2019  
Addition of ACC Statin Intolerance App to regulatory status

June 2019  
Annual review and reference update
This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 20, 2019 and is effective on July 1, 2019.