

5.40.08

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Last Review Date: June 16, 2022

Repatha

Description

Repatha (evolocumab)

Background

Repatha (evolocumab) is a human monoclonal antibody that binds to proprotein convertase subtilisin kexin type 9 (PCSK9). PCSK9 binds to the low-density lipoprotein cholesterol (LDL-C) receptors (LDLR) on the surface of hepatocytes to promote LDLR degradation within the liver. By blocking PCSK9's ability to work, more receptors are available to clear LDL cholesterol from the blood, thereby lowering LDL cholesterol levels (1).

Regulatory Status

FDA-approved indications: Repatha is a PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) inhibitor antibody indicated: (1)

1. in adults with established cardiovascular disease (CVD) to reduce the risk of myocardial infarction, stroke, and coronary revascularization.
2. 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.
3. as an adjunct to diet and other LDL-C-lowering therapies in pediatric patients aged 10 years and older with HeFH, to reduce LDL-C.
4. as an adjunct to other LDL-C-lowering therapies in adults and pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia (HoFH), to reduce LDL-C

Physicians often measure creatine kinase (CK) in patients about to begin statins or already on statins. CK is an enzyme that leaks out of damaged muscle. Many physicians will not start or

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continue statins to lower LDL-C in asymptomatic patients with high CK because of concern regarding possible statin-induced myositis-rhabdomyolysis. High pretreatment CK, predominantly 1 to 5 times the upper normal limit (UNL), should not be an impediment to start or continue statins to lower LDL-C (2).

Spectrum of statin-associated muscle adverse events: (3)

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 \geq 10-fold greater than untreated baseline CK levels or normative upper limit that are adjusted for age, race, and sex
 - Severe \geq 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 \geq 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: (4)

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

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

The safety and effectiveness of Repatha have not been established in pediatric patients with HoFH or HeFH who are younger than 10 years of age or in pediatric patients with other types of hyperlipidemia (1).

Related policies

Evkeeza, Juxtapid, Nexletol Nexlizet, 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** for the treatment of homozygous familial hypercholesterolemia (HoFH), heterozygous familial hypercholesterolemia (HeFH), or for patients that have atherosclerotic cardiovascular disease; and if the conditions indicated below are met.

Repatha may be considered **investigational** 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. 10 years of age 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

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- d. Provided documentation (medical records, laboratory reports) of baseline and/or current LDL-C level \geq 100 mg/dL in the past 90 days
2. Heterozygous familial hypercholesterolemia (HeFH)
- a. 10 years of age and older
 - b. Provided documentation (medical records, laboratory reports) of baseline and/or current LDL-C level \geq 100 mg/dL in the past 90 days

AND ONE of the following for HeFH:

- a. Provided documentation (medical records, patient's chart) of confirmed diagnosis by LDL-R DNA Sequencing Test or APOB (hypercholesterolemia) Mutation Analysis
 - b. Dutch Lipid Clinic Network Criteria score $>$ 5
 - c. Simon-Broome Diagnostic Criteria for definite familial hypercholesterolemia
3. Atherosclerotic cardiovascular disease (ASCVD)
- a. 18 years of age 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%

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AND ALL of the following for **ALL** diagnoses:

1. Patient will be assessed for response (i.e., LDL-C reduction) and adherence to the prescribed lipid lowering regimen after 3 months
2. **NO** dual therapy with another proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, Nexletol/Nexlizet, Juxtapid, or Evkeeza

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 (i.e., more than 2 weeks) muscle symptoms (e.g., 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
 - i. 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 (e.g., 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
 - c. Severe allergic reaction to a statin (e.g., anaphylaxis, angioedema, severe rash)

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,

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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)
 - a. 10 years of age and older
2. Homozygous familial hypercholesterolemia (HoFH)
 - a. 10 years of age and older
3. Atherosclerotic cardiovascular disease (ASCVD)
 - a. 18 years of age and older

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 (\geq) 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 (PCSK9) inhibitor, Nexletol/Nexlizet, Juxtapid, or Evkeeza

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.

| High-Intensity Statin Therapy | Moderate-Intensity Statin Therapy | Low-Intensity Statin Therapy |
|---|---|---|
| Atorvastatin (Lipitor) 40 – 80 mg a day Rosuvastatin (Crestor) 20 – 40mg a day | Atorvastatin (Lipitor) 10 – 20mg a day Rosuvastatin (Crestor) 5 - 10mg a day | Simvastatin (Zocor) 10mg a day Pravastatin (Pravachol) 10 - 20mg a day |

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| <p>Simvastatin (Zocor) 80 mg a day</p> | <p>Simvastatin (Zocor) 20 - 40mg a day</p> <p>Pravastatin (Pravachol) 40 - 80mg a day</p> <p>Lovastatin (Mevacor) 40mg a day</p> <p>Fluvastatin XL (Lescol XL) 80mg a day</p> <p>Fluvastatin (Lescol) 40mg twice a day</p> <p>Pitavastatin (Livalo) 2 - 4mg a day</p> | <p>Lovastatin (Mevacor) 20mg a day</p> <p>Fluvastatin (Lescol) 20 - 40mg a day</p> <p>Pitavastatin (Livalo) 1mg a day</p> |
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Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Quantity

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|---------------|--|
| Repatha 140mg | 9 syringes or auto-injectors per 84 days OR |
| Repatha 420mg | 6 syringes per 84 days |

Duration 12 months

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary

Repatha (evolocumab) is a human monoclonal antibody that binds to proprotein convertase subtilisin kexin type 9 (PCSK9). PCSK9 binds to the low-density lipoprotein cholesterol (LDL-C) receptors (LDLR) on the surface of hepatocytes to promote LDLR degradation within the liver. By blocking PCSK9's ability to work, more receptors are available to clear LDL cholesterol from the

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blood, thereby lowering LDL cholesterol levels. The safety and effectiveness of Repatha have not been established in pediatric patients with HoFH and HeFH who are younger than 10 years of age. The safety and effectiveness of Repatha have not been established in pediatric patients with primary hyperlipidemia (1).

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

References

1. Repatha [package insert]. Thousand Oaks CA: Amgen Pharmaceuticals Inc.; September 2021.
2. Glueck CJ et al. Should high creatine kinase discourage the initiation or continuance of statins for the treatment of hypercholesterolemia. *Metab Clin Exp*. 2009;58:233–238.
3. Rosenson R, Baker S, et al. An assessment by the Statin Muscle Safety Task Force: 2014 update. *Jrnl Clin Lipid*, 2014; 8, S58-S71.
4. Banach M, Rizzo M, et al. Statin intolerance - an attempt at a unified definition. Position paper from an International Lipid Expert Panel. *Arch Med Sci* 2015; 11, 1: 1-23.

Policy History

| Date | Action |
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| 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 (e.g., muscle pain, weakness, cramps) with ALL of the following- to ONE 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 |

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| 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 Tool to regulatory status |
| June 2019 | Annual review and reference update |
| June 2020 | Annual review |
| September 2020 | Annual review |
| March 2021 | Addition of requirement: no dual therapy with Nexletol/Nexlizet. Addition of contraindication to statins to include severe allergic reaction to a statin (e.g., anaphylaxis, angioedema, severe rash) |
| June 2021 | Annual editorial review and reference update. Revised dual therapy requirement to include not dual therapy with Evkeeza. |
| October 2021 | Changed age requirement for HeFH and HoFH to 10 years of age and older per latest package insert. Increased the quantity limit for 420mg to 6/84 to allow for new dosing. Also changed the 140mg to 9/84 from 9/90. |
| December 2021 | Annual review |
| June 2022 | Annual review |

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 16, 2022 and is effective on July 1, 2022.