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Section:	Prescription Drugs	**Effective Date:**	April 1, 2024
Subsection:	Cardiovascular Agents	**Original Policy Date:**	September 9, 2015
Subject:	Repatha	**Page:**	1 of 10

Last Review Date: March 8, 2024

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 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 3 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

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* 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, Leqvio, 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** 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 for HoFH:
   a. 10 years of age and older
   b. 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 drawn LDL-C level ≥ 100 mg/dL in the past 6 months

2. Heterozygous familial hypercholesterolemia (HeFH)
   a. 10 years of age and older
   b. Provided documentation (medical records, laboratory reports) of drawn LDL-C level ≥ 100 mg/dL in the past 6 months

   AND ONE of the following for HeFH:
   a. 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. Provided documentation (medical records, laboratory report) of drawn LDL-C level ≥ 70 mg/dL in the past 6 months

   AND ONE of the following for ASCVD:
   a. Patient has had at least **ONE** of the following atherosclerotic cardiovascular disease (ASCVD) or cardiovascular events:
      i. Acute coronary syndrome (ACS)
      ii. Myocardial infarction (MI)
      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 (PAD) 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 ≥ 7.5%
      ii. Framingham Risk Score: score ≥ 20%

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

1. Patient will be assessed for response (i.e., LDL-C reduction) and adherence to the prescribed lipid lowering regimen after 3 months
2. Documentation of an inadequate treatment response to 3 months of at least **ONE** high intensity statin **OR** patient has an intolerance or contraindication to statin therapy
3. **NO** dual therapy with another Prior Authorization (PA) lipid lowering agent (see Appendix 1)

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)
    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. Patient has had **ONE** of the following:
    i. Percentage reduction of LDL-C level is ≥ 40%, compared to the level immediately prior to starting a PCSK9 inhibitor
    ii. Absolute LDL-C < 100mg/dL
b. Patient will be assessed for adherence to the prescribed lipid lowering regimen
c. **NO** dual therapy with another Prior Authorization (PA) lipid lowering agent (see Appendix 1)

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)** 20 - 40mg a day **Pravastatin (Pravachol)** 40 - 80mg a day **Lovastatin (Mevacor)** 40mg a day **Fluvastatin XL (Lescol XL)** 80mg a day **Fluvastatin (Lescol)** 40mg twice a day **Pitavastatin (Livalo)** 2 - 4mg a day	**Simvastatin (Zocor)** 10mg a day **Pravastatin (Pravachol)** 10 - 20mg a day **Lovastatin (Mevacor)** 20mg a day **Fluvastatin (Lescol)** 20 - 40mg a day **Pitavastatin (Livalo)** 1mg a day

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Quantity

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 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
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
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

September 2022	Annual review. Per SME, revised regulatory status and removed simvastatin 80mg from the statins list
October 2022	Removed required documentation for HoFH and HeFH LDL-R DNA Sequencing Test or APOB Mutation Analysis. Revised initiation LDL-C levels to drawn level in the past 6 months. Removed required documentation for an ASCVD event or high-risk score. Revised requirements for statin inadequate response and intolerances (myalgia, myositis, and hepatotoxicity). Removed required documentation for renewal LDL level
March 2023	Annual editorial review. Revised wording of no dual therapy requirement for consistency and added Appendix 1
March 2024	Annual review

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 8, 2024 and is effective on April 1, 2024.

Appendix 1 - List of PA Lipid Lowering Agents

Generic Name	Brand Name
alirocumab	Praluent
bempedoic acid	Nexletol
bempedoic acid/ezetimibe	Nexlizet
evolocumab	Repatha
inclisiran	Leqvio
lomitapide	Juxtapid

*Dual therapy with Evkeeza (evinacumab-dgnb) is allowed