



RATIONALE FOR INCLUSION IN PA PROGRAM

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. to reduce the risk of major adverse cardiovascular (CV) events (CV death, myocardial infarction, stroke, unstable angina requiring hospitalization, or coronary revascularization) in adults with established cardiovascular disease (CVD).
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”.



REPATHA
(evolocumab)

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).

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.; November 2024.
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. Accessed on April 2, 2021.
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. Accessed on April 2, 2021.
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. Accessed on April 2, 2021.