RATIONALE FOR INCLUSION IN PA PROGRAM

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)

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.

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