

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125522Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management
RISK EVALUATION AND MITIGATION STRATEGY REVIEW**

Date: July 10, 2015

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Division of Risk Management (DRISK)

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Subject: Review to determine if a REMS is necessary

Drug Name(s): Repatha (Evolocumab)

Therapeutic class & dosage form: Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor
Subcutaneous injection via Pen

OND Review Division Division of Metabolism and Endocrinology Products

Application Type/Number: BLA 125522

Application received August 27, 2014

PDUFA/Action Date August 27, 2015

Applicant/sponsor: Amgen

OSE RCM #: 2014-1868

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1 INTRODUCTION

This review by the Division of Risk Management evaluates if a risk evaluation and mitigation strategy (REMS) is needed for Repatha (evolocumab).

The proposed indications for Repatha are:

- For treatment of adults with primary hyperlipidemia (heterozygous familial and nonfamilial) or mixed dyslipidemia, as an adjunct to diet to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non-HDL-C), TC/HDL-C, ApoB/apolipoprotein A1 (ApoA1), very low density lipoprotein cholesterol (VLDL-C), triglycerides (TG) and lipoprotein (a) (Lp[a]), and to increase HDL-C and ApoA1:
 - in combination with a statin or statin with other lipid lowering therapies (e.g., ezetimibe), or
 - alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or
 - alone or in combination with other lipid-lowering therapies in patients for whom a statin is not considered clinically appropriate.
- For treatment of patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C, TC, ApoB, and non-HDL-C in combination with other lipid lowering therapies (e.g., statins, LDL apheresis).

Amgen did not propose a REMS for Repatha.

1.1 BACKGROUND

Evolocumab is a human monoclonal immunoglobulin G2 (IgG2) antibody that inhibits circulating PCSK9 from binding to low-density lipoprotein receptors (LDLR) on the liver cell surface. This prevents PCSK9-mediated LDLR degradation, which leads to increases in LDL receptors, which results in decreases in serum LDL cholesterol.¹ This is a novel mechanism of action for cholesterol lowering agents. Amgen submitted an NDA for Repatha (evolocumab) August 27, 2014. The sponsor proposes marketing Repatha as a 140-mg prefilled syringe, and as a 140-mg prefilled autoinjector. The proposed dosage is 140 mg every 2 weeks or 420 mg once monthly for primary hyperlipidemia and mixed dyslipidemia, and 420 mg once monthly or every two weeks for homozygous familial hypercholesterolemia. Dosages of 420 mg require 3 consecutive 140 mg injections.

1.2 REGULATORY HISTORY

The following are regulatory milestones important to this application

- January 24, 2014—pre-BLA meeting

¹ Information from the Background section from Dr. Craig's summary presented in the clinical briefing document for the June 10, 2015 EMDAC Advisory Committee.

- August 27, 2014—BLA received
- June 10, 2015— FDA Endocrine and Metabolic Drugs Advisory Committee (EMDAC) meeting to discuss application
- August 27, 2015—action date under the *Prescription Drug User Fee Act* (PDUFA)

2 MATERIALS REVIEWED

We reviewed the following from the application submitted August 27, 2014:

- Clinical Overview
- Proposed draft labeling

Additionally, we reviewed the following:

- Draft labeling as edited by FDA as of May 14, 2015
- Discipline handouts from midcycle meeting for application, January 29, 2015
- Mid-cycle communication with sponsor, April 1, 2015
- FDA clinical briefing document for June 10, 2015 EMDAC Advisory Committee Meeting, Dr. Eileen Craig

3 RESULTS OF REVIEW

3.1 OVERVIEW OF DEVELOPMENT PROGRAM ²

Evolocumab was studied in four double-blind, randomized, placebo- or ezetimibe-controlled 12-week trials and one 52-week placebo-controlled trial. The four 12-week trials evaluated evolocumab in four different patient populations: (1) monotherapy in a population at low risk of cardiovascular events ((N=614); (2) in combination with statins (N=1896); (3) in ‘statin-intolerance’ (N=307); and, (4) in heterozygous familial hypercholesterolemia (HeFH) (N=329). The 52-week trial (N=901: 599 evolocumab; 302 placebo) also evaluated evolocumab in four different patient populations whose background therapy was based upon their screening LDL-C, risk category according to the categorization by the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III), and statin therapy: (1) no drug therapy required - diet alone; (2) low dose drug therapy required - diet plus atorvastatin 10 mg; (3) high dose drug therapy required - diet plus atorvastatin 80 mg; and, (4) maximal drug therapy required - diet plus atorvastatin 80 mg plus ezetimibe 10 mg.

² Information in Overview of Development Program adapted from Dr. Craig’s summary presented in the clinical briefing document for the June 10, 2015 EMDAC Advisory Committee.

Analyses from the four 12-week trials in primary hyperlipidemia demonstrated statistically significant reductions in LDL-C with evolocumab ($p < 0.001$).

In the placebo-controlled HoFH trial, 21 (43%) of the patients had coronary artery disease, and 4 (8%) had cerebrovascular or peripheral arterial disease. Baseline therapy included a statin for all patients; the trial did not permit lipid apheresis treatment. Evolocumab, compared to placebo, significantly reduced LDL-C from baseline to Week 12 by 31%.

3.2 SAFETY CONCERNS³

The safety database comprises data from 5710 patients who received evolocumab in all trials. As of April 1, 2014, 5416 patients had received evolocumab for at least 3 months, 1824 patients for at least 12 months, and 614 patients for 2 years or more. Patients treated with evolocumab for at least 1 year included 345 with established CVD, 183 with diabetes, 463 on high doses of a statin, and 439 who were 65 years of age or older.

Fifteen deaths were reported in the clinical program. Eleven deaths were categorized as cardiovascular; there was no difference in incidence of cardiovascular deaths between evolocumab-treated patients and patients in the control groups. Deaths not categorized as cardiovascular included a patient who received evolocumab who died from a clostridium difficile infection, a patient who received evolocumab who died from an unknown cause, a patient who received evolocumab who died from lung cancer, and a patient who received evolocumab who died from cholangio-carcinoma.

The most common serious adverse events were myocardial infarction (0.1% in patients receiving evolocumab and 0% in control patients), angina pectoris (0.1% in both groups), and pneumonia (0.1% and 0%). There was a numeric increase in the evolocumab group in the incidence of cardiac disorders, pancreatitis, appendicitis, pneumonia and back pain.

The incidence of adverse events leading to discontinuation was slightly higher in the evolocumab group as compared to the placebo group. Small increases in discontinuations in the evolocumab group as compared to the any control group were due to cardiac disorders, increased creatine phosphokinase, and nausea.

Frequently occurring adverse events were similar for patients receiving evolocumab and patients in control groups. The most common adverse events that occurred more frequently in patients receiving evolocumab were nasopharyngitis (5.9% in patients receiving evolocumab and 4.8% in control patients), upper respiratory tract infection (3.2% and 2.7%), back pain (3.0% and 2.7%), and nausea (2.1% and 1.8%).

Cardiovascular events were reported in 77 (2.4%) in patients receiving evolocumab and 29 (1.4%) patients in any control group. The most common adverse events in the evolocumab group and any control group were palpitations (0.6% and 0.3%), angina pectoris (0.3% and 0.2%), and ventricular extrasystoles (0.3% and 0.1%). Serious cardiac adverse events were reported in 21 (0.7%) participants in the evolocumab group and 5

³ Information in Safety Concerns adapted from Dr. Craig's summary presented in the clinical briefing document for the June 10, 2015 EMDAC Advisory Committee

(0.2%) participants in the any control group. The most common serious cardiac events in the evolocumab group and any control group were myocardial infarction (0.1% and 0%), angina pectoris (0.1% and 0.1%), and acute myocardial infarction (0.1% and 0%).

An imbalance was observed in cases of pancreatitis (6 events in patients receiving evolocumab and 2 events in control patients). All events resolved; 3 events resolved while the patient continued to receive evolocumab. Other risk factors identified in these cases included concurrent alcohol use, diabetes, gallstones, and concomitant medications associated with pancreatitis.

In patients with impaired fasting glucose at baseline, there was a small increase in new-onset diabetes in patients receiving evolocumab. This increase was not observed in patients receiving evolocumab with normal baseline glucose levels.

An imbalance was observed in cases of serious renal disorders (acute glomerulonephritis, minimal lesion glomerulonephritis, IgA nephropathy, and acute renal failure) and proteinuria in statin-intolerant and diabetic subjects. These events occurred in 4 (0.1%) patients receiving evolocumab compared with no such events in control patients.

Arthralgia occurred more frequently in patients receiving evolocumab (3.1%) compared to patients receiving control (2.7%). Likewise, back pain occurred more frequently in patients receiving evolocumab (3.4%) compared to patients receiving control (2.5%).

The incidences of transaminase and bilirubin abnormalities were low and similar in the control and evolocumab groups. Three (0.1%) patients treated with evolocumab had hepatic transaminase levels 3 times the upper limit of normal and total bilirubin over 2 times the upper limit of normal or elevated INR. Additional potentially confounding factors in the cases are as follows:

- patient with concomitant alcohol abuse
- patient with elevated INR due to warfarin; evolocumab was continued and hepatic transaminases declined
- patient receiving nitrofurantoin and simvastatin concomitantly; liver biopsy was consistent with drug-induced hepatitis; hepatic transaminases returned to normal after discontinuation of nitrofurantoin, evolocumab, and simvastatin

There was an imbalance in hypersensitivity events in patients receiving evolocumab, including 5 cases of angioedema.

3.3 RISK MANAGEMENT PROPOSED BY THE SPONSOR

The sponsor did not propose a REMS for Repatha.

4 EMDAC CONSIDERATION OF THE APPLICATION

EMDAC convened June 10, 2016 to consider the NDA for Repatha. Committee members agreed that Repatha is effective in decreasing LDL-C. The committee members agreed that some potential safety issues have not been sufficiently explored in the clinical trials;

the issues insufficiently explored are pancreatitis, hypersensitivity, new-onset diabetes in patients with baseline impaired fasting glucose, musculoskeletal adverse events, hepatic transaminase elevations, hepatobiliary adverse events, and unknown possible events related to chronically low LDL-C. Committee members agreed that none of the safety concerns currently represent a safety signal based on the limited data available to date.

The committee voted Yes-11, No-4 on the following question: Has the applicant sufficiently established that the LDL-C-lowering benefit of evolocumab exceeds its risks to support approval in one or more patient populations (excluding HoFH)? The committee members who voted “no” cited the lack of long-term safety data, the lack of cardiovascular outcomes data, and the concern that approval of Repatha would undermine participation in the ongoing cardiovascular outcomes trial. Other committee members agreed with these concerns, but cited compelling need in the HeFH patient population as the basis to favor approval of the application. Committee members who favored approval of the application generally voiced support for use of evolocumab only by patients at moderate-to-high risk for cardiovascular events as demonstrated by a diagnosis of HeFH, or by the presence of cardiovascular risk factors, and high LDL-C that cannot be sufficiently reduced with statins.

The committee voted unanimously “yes” on the following question: Has the applicant sufficiently established that the LDL-C-lowering benefit of evolocumab exceeds its risks to support approval for homozygous familial hypercholesterolemia?

5 DISCUSSION OF A REMS

The clinical review to date has identified several potential safety issues with evolocumab, including pancreatitis, renal adverse events, new-onset diabetes, musculoskeletal adverse events, hepatotoxicity, hypersensitivity, and cardiovascular events. DMEP has tentatively determined that the *Warnings and Precautions* section of the labeling will likely include

(b) (4) allergic reactions.
(b) (4)

are not included in the draft labeling. The lack of information about cardiovascular outcomes is included as a limitation of use in the draft labeling. If Repatha is approved for commercial marketing, it is likely the potential safety issues identified will be studied in the post-approval setting, including in the ongoing cardiovascular outcomes trial.

While EMDAC members voiced support for use of Repatha only in patients with HeFH, HoFH, and in other patients at moderate-to-high risk for cardiovascular events, there was not unanimity on the patient population that should be prescribed Repatha pending the availability of longer term safety data. Some committee members believed that only patients with HoFH or HeFH should be prescribed Repatha pending availability of longer term safety data, while other committee members cited support for use in other patients (e.g., patients with mixed dyslipidemia) with elevated LDL-C levels at moderate-to-high risk for cardiovascular events. The nuanced discussion of the known risks and benefits of treatment with evolocumab, and the limitations of the safety database would be best

presented in the labeling. At this time a REMS is not necessary to ensure the benefits outweigh the risks for the aforementioned risks.

It appears the potential safety issues identified in this application can be communicated with labeling and through post-marketing pharmacovigilance.

6 CONCLUSION/RECOMMENDATION

The indication statement has not been negotiated with the sponsor; however, the sponsor is requesting the following indication statement:

Repatha is indicated in adults with primary hyperlipidemia (heterozygous familial and nonfamilial) or mixed dyslipidemia, as an adjunct to diet to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non-HDL-C), TC/HDL-C, ApoB/apolipoprotein A1 (ApoA1), very low density lipoprotein cholesterol (VLDL-C), triglycerides(TG) and lipoprotein (a) (Lp[a]), and to increase HDL-C and ApoA1:

- in combination with a statin or statin with other lipid lowering therapies (e.g., ezetimibe), or
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or
- alone or in combination with other lipid-lowering therapies in patients for whom a statin is not considered clinically appropriate,

Based on the current safety information a REMS would not be necessary to ensure the benefits outweigh the risks for requested indications.

We ask that DRISK be included in the discussions of safety concerns with Repatha.

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/s/

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