CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761181Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761181
PDUFA Goal Date	February 21, 2021
OSE RCM #	2020-410 and 2020-1241
Reviewer Name	Mei-Yean Chen, Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Deputy Division Director	Doris Auth, Pharm.D.
Review Completion Date	January 6, 2021
Subject	Evaluation of Need for a REMS
Established Name	Evinacumab-dgnb
Trade Name	Evkeeza
Name of Applicant	Regeneron Pharmaceuticals Inc.
Therapeutic Class	An angiopoietin-like 3 (ANGPTL3) inhibitor antibody
Formulation(s)	Injection: 345 mg/2.3 mL (150 mg/mL) solution in single-dose vial and 1200 mg/8 mL (150 mg/mL) solution in single-dose vial
Dosing Regimen	15 mg/kg intravenously once every 4 weeks

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Evkeeza (evinacumab-dgnb) is necessary to ensure the benefits outweigh its risks. Regeneron Pharmaceuticals, Inc. submitted a Biologic License Application (BLA) 761181 for Evkeeza (evinacumab-dgnb) with the proposed indication as an adjunct to other low-density lipoprotein-cholesterol (LDL-C) lowering therapies for the treatment of adults and pediatric patients aged 12 years and older with homozygous familial hypercholesterolemia (HoFH), with the following Limitations of Use:

- The safety and effectiveness of Evkeeza have not been established in patients with other causes of hypercholesterolemia, including those with heterozygous familial hypercholesterolemia (HeFH).
- The effect of Evkeeza on cardiovascular morbidity and mortality has not been determined.

The risks associated with Evkeeza include serious hypersensitivity reactions and embryo-fetal toxicity. The applicant did not submit a proposed REMS or risk management plan with this application.

Division of Risk Management (DRM) and Division of Diabetes, Lipid disorders, and Obesity (DDLO) determined that a REMS is not needed to ensure the benefits of Evkeeza outweigh its risks.

There still exists an unmet clinical need for new therapies that reduce LDL-C and the risk for premature atherosclerotic cardiovascular disease (ASCVD) for patients with HoFH. In the clinical trials of Evkeeza, there was a 49% additional LDL-C reduction which occurred at 24 weeks, and the effect was sustained throughout to 48 weeks. Evkeeza provides a therapeutic option for patients with HoFH with a reasonable safety profile. The serious risks associated with Evkeeza are serious hypersensitivity reactions and embryo-fetal toxicity. These risks will be communicated in the Warnings and Precautions section of the labeling if the product is approved. Evkeeza will likely be prescribed by internal medicine physicians, cardiologists, endocrinologists, lipid specialists and pediatric lipid specialists who are familiar with these risks and how to manage them.

1. INTRODUCTION

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] Evkeeza is necessary to ensure the benefits outweigh its risks. Regeneron Pharmaceuticals, Inc. submitted a Biologic License Application (BLA) 761181 for Evkeeza (evinacumab-dgnb) with the proposed indication as an adjunct to other low-density lipoprotein-cholesterol (LDL-C) lowering therapies for the treatment of adults and pediatric patients aged 12 years and older with homozygous familial hypercholesterolemia (HoFH), with the following Limitations of Use:

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity*

- The safety and effectiveness of Evkeeza have not been established in patients with other causes of hypercholesterolemia, including those with heterozygous familial hypercholesterolemia (HeFH).
- The effect of Evkeeza on cardiovascular morbidity and mortality has not been determined.

This application is under review in the Division of Diabetes, Lipid disorders, and Obesity (DDLO). The applicant did not submit a proposed REMS or risk management plan with this application.

2. BACKGROUND

2.1 PRODUCT INFORMATION

Evkeeza (evinacumab-dgnb), a new molecular entity, is an angiopoietin-like protein 3 (ANGPTL3) inhibitor monoclonal antibody produced by recombinant DNA technology in Chinese hamster ovary cell suspension culture. Evkeeza binds to and inhibits ANGPTL3, which is a member of the angiopoietin-like protein family that is expressed in the liver and plays a prominent role in the regulation of lipid metabolism by inhibiting lipoprotein lipase (LPL) and endothelial lipase (EL). Evkeeza inhibition of ANGPTL3 leads to reduction in LDL-C, high density lipoprotein-cholesterol (HDL-C), and triglycerides. Evkeeza injection is supplied as 345 mg/2.3 ml or 1200 mg/8 ml single-use vial. The recommended dose is 15 mg/kg administered by intravenous (IV) infusion over 60 minutes every 4 weeks. Evkeeza is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761181 relevant to this review:

- November 2012: Investigation New Drug (IND) opened
- February 2016: Orphan drug for treatment of HoFH designated
- March 2017: Breakthrough therapy for treatment of HoFH designated
- October 2019: pre-BLA meeting agreed on size of safety database and timeline for 120-day safety update
- February 2020: Rolling review granted
- June 2020: Final part of rolling review received
- September 23, 2020: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for Evkeeza.

3 THERAPEUTIC CONTEXT AND TREATMENT OPTIONS

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Familial hypercholesterolemia (FH) is a common autosomal codominant genetic disease. Heterozygous FH (HeFH) is estimated to occur in about 1 in 200 to 300 individuals. Homozygous Familial Hypercholesterolemia (HoFH) is very rare with an estimated prevalence of about 1:300,000 to 1: 400,000[1]. Homozygous familial hypercholesterolemia is a serious genetic condition resulting in severely elevated LDL-C and accelerated cardiovascular disease (CVD). The most common mutation genes to cause HoFH are low-density lipoprotein receptor (LDLR) gene, proprotein convertase subtilisin kexin type 9 (PCSK9) gene, and apolipoprotein B (APOB). More than 90% of HoFH results from LDLR mutations. The amount of residual LDLR activity that a patient has contributes to the severity of disease. The lower the activity, the more severe the disease and the harder to treat with the available treatment options. LDL-C levels in patients with HoFH are usually higher than 500 mg/dL. This lifelong exposure to extremely elevated LDL-C leads to an exceedingly high risk of developing premature atherosclerosis, valvular stenosis, and supravalvular stenosis. This accelerated atherosclerosis results in premature atherosclerotic cardiovascular disease (ASCVD) and increased risk for cardiovascular (CV) events. Patients may begin to have myocardial infarction in their second decade of life and have a decreased life expectancy of mid-40s. The clinical diagnosis of HoFH[2] is based on untreated LDL-C> 500 mg/dL or treated LDL-C ≥300 mg/dL, plus either of the following:

- Cutaneous or tendon xanthoma before age 10 years, or
- Elevated LDL-C levels consistent with HeFH in both parents.

Cardiovascular disease is the leading cause of death in the United States (US)[b] affecting over one third of Americans.[3] Heart attack and stroke are usually caused by ASCVD. Atherosclerotic cardiovascular disease develops because of a buildup of sticky cholesterol-rich plague. The plaque can harden and narrow the arteries as patients age. Elevated levels of LDL-C are associated with an increased risk of CVD events and lowering of LDL-C is associated with a reduction in these events. LDL-C level is an important modifiable risk factor for ASCVD. A meta-analysis of data from 14 randomized trials of statins demonstrated that lower LDL-C can significantly reduce the incidence of CVD in a wide range of patients[4].

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The 2018 American Heart Association /American Chest Association treatment guidelines for LDL-C reduction, in addition to adherence of a healthy lifestyle[5], includes statins, Ezetimibe, Alirocumab (a PCSK9 inhibitor), Evolocumab (a PCSK9 inhibitor), and bile acid sequestrants.

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[b] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.

[b] Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.

Lomitapide (trade name Juxtapid), a microsomal triglyceride transfer protein inhibitor, was approved by the FDA in 2012 as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce LDL-C, total cholesterol, apolipoprotein B, and non-HDL-C in patients with HoFH. The safety issues associated with lomitapide include high rates (93%) of gastrointestinal side effects and hepatic abnormalities such as hepatic steatosis and abnormalities in liver function tests.[6] A REMS with elements to assure safe use (ETASU) was required for Lomitapide [7] to ensure the benefits outweigh the potential risk of hepatotoxicity.[8]

Patients with HoFH could potentially benefit from lipid apheresis, but many patients do not receive it due to the lack of qualified lipoprotein apheresis centers[9] (there are only about 60 lipoprotein apheresis centers in the United States), the burden of weekly or every 2 weeks apheresis sessions (lasting 1.5 to 3 hours per session), the costs associated with apheresis treatment, and tolerability issues the procedure.

Patients with HoFH have markedly elevated LDL-C and rarely meet their target LDL-C, even with multiple lipid-lowering medications. There still exists an unmet clinical need for new therapeutic options that reduce LDL-C and the risk for premature ASCVD.

4 BENEFIT ASSESSMENT

Study ELIPASE-HoFH (NCT 03399786) was a multi-center, randomized, double-blind, placebo-controlled trial that evaluated efficacy of Evkeeza compared to placebo in 65 patients with HoFH.[10] The time period included a 24-week double-blind treatment period and a 24-week open-label treatment period. In the double-blind period, 43 patients were randomized to receive Evkeeza 15 mg/kg IV every 4 weeks and 22 patients received placebo. Patients were on a background of other lipid-lowering therapies (including maximally-tolerated statins, ezetimibe, PCSK9 inhibitors, lomitapide, and lipoprotein apheresis). The diagnosis of HoFH was determined by genetic testing or by the presence of the following criteria: history of an untreated triglyceride (TC) greater than 500 mg/dL and either xanthoma before 10 years of age or evidence of TC greater than 250 ml/dL in both parents. The mean LDL-C at baseline was 255 mg/dL and 55% of patients had baseline LDL-C at least 190 mg/dL or more. At baseline, 94% of patients were on statins, 75% on ezetimibe, 77% on a PCSK9 inhibitor antibody, 22 % on lomitapide, and 34% were receiving lipoprotein apheresis. The mean age was 42 years (range 12 to 75) with 54% women, 3% Hispanic, 74% White, 15% Asian, 3% Black, and 8% other or not reported.

The primary end-point was percent change in LDL-C from baseline to week 24. At week 24, the least squares (LS) mean treatment difference between Evkeeza and placebo in mean percent change (decrease) in LDL-C from baseline was -49% (95% confidence interval [CI]: -65.0% to -33.1%; p<0.0001). At week 24, the absolute LS mean change in LDL-C from baseline for patients receiving Evkeeza was -134.7 mg/dL, compared to -2.6 mg/dL for patients receiving placebo (treatment difference -132.1; 95% CI: -175.3 to -88.9; p<0.0001).

In the ELIPSE-HoFH trial, one pediatric patient (15 years old) received 15 mg/kg IV of evkeeza every 4 weeks and one pediatric patient received placebo, as an adjunct to other lipid-lowering therapies (statins, ezetimibe, PCSK9 inhibitors, and lipoprotein apheresis). At week 24, the percent change in LDL-C with Evkeeza was -73.3% and with placebo +60%. In an open label extension study, 13 pediatric

patients with HoFH (12 to 17 years of age) received 15 mg/kg IV of evkeeza every 4 weeks as an adjunct to other lipid lowering therapies (statins, ezetimibe, PCSK9 inhibitors, and lipoprotein apheresis) for a median treatment duration of 33 weeks. The mean percent change from baseline in LDL-C at week 24 was -52%.

The medical officer communicated at the midcycle meeting that there was a 49% additional LDL-C reduction at 24 weeks when added to a maximally-tolerated statin, ezetimibe, and PCSK9 inhibitor.[11] The effects sustained throughout treatment to 48 weeks. The medical officer also stated that Evkeeza appeared to be effective in three pediatric patients (age 12, 12, and 15).

5 RISK ASSESSMENT & SAFE-USE CONDITIONS

The safety of Evkeeza was based on pooled data from two randomized, double-blind, placebo-controlled trials that included 81 patients treated with Evkeeza for 24 weeks. The mean age for Evkeeza-treated patients was 50 years (range 5 to 75 years), 56% were women, 85% were White, 2% Black, 6% Asian, and 9% Hispanic. Forty-four (38%) Evkeeza-treated patients had HoFH, 60 (51%) had non-familial hyperlipidemia with established ASCVD. Patients received Evkeeza 15 mg/kg IV every 4 weeks as add-on therapy to other lipid-lowering therapies, including maximally-tolerated statin, ezetimibe, PCSK9 inhibitors, lomitapide, and apheresis. The followings are the risks[c] associated with the use of Evkeeza that will be included in Warnings and Precautions of the label. [10]

5.1 SERIOUS HYPERSENSITIVITY REACTIONS

Anaphylaxis was reported in one (1%) patient and infusion reactions (e.g., rash, pyrexia, headache, weakness, fatigue, nausea, and nasal congestion) were reported in nine patients treated with Evkeeza versus two patients treated with placebo, respectively. The patient with the anaphylaxis reaction had a medical history of asthma and allergic rhinitis. Within five minutes of the second dose, she developed flushed face and chest, hypotension, shortness of breath, dizzy, and racing heart. Her symptoms resolved after the infusion was stopped and oral diphenhydramine was given.

Healthcare providers (HCPs) will be advised to discontinue Evkeeza if signs or symptoms of serious hypersensitivity reactions occur, treat according to the standard care, and monitor until signs and symptoms resolve.

5.2 EMBRYO-FETAL TOXICITY

Evkeeza may cause fetal harm when administered to pregnant patients based on the data in animal reproduction studies. Administration of Evkeeza to rabbits during organogenesis caused increases in fetal malformations at doses below the human exposure.

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[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

If approved, HCPs will be advised to educate patients who may become pregnant of the risk to a fetus and obtain a pregnancy test prior to initiating the therapy. Patients will be consulted to use effective contraception during therapy and for at least five months following the last dose.

6 EXPECTED POSTMARKET USE

If approved, Evkeeza will be used in outpatient infusion centers and home care infusion settings. The likely prescribers will be internal medicine physicians, cardiologists, endocrinologists, lipid specialists and pediatric lipid specialists.

7 RISK MANAGEMENT ACTIVITIES PROPOSED BY THE APPLICANT

The Applicant did not propose any risk management activities for Evkeeza beyond routine pharmacovigilance and labeling.

8 DISCUSSION OF NEED FOR A REMS

The Clinical Reviewer recommends approval of Evkeeza based on the efficacy and safety information currently available. DRM and DDLO agree that a REMS is not necessary to ensure the benefits of Evkeeza outweigh its risks. When evaluating factors of a REMS is necessary to ensure that the benefits outweigh the risks for Evkeeza, this reviewer considered the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and prescribing population.

Homozygous familial hypercholesterolemia is estimated to occur in about 1 in 300,000-400,000 individuals in the United States. Cardiovascular disease is the leading cause of death in the United States. Elevated levels of LDL-C are associated with an increased risk of CVD events and lowering of LDL-C is associated with a reduction in CVD events. In the clinical trials of Evkeeza, there was a 49% additional LDL-C reduction which occurred at 24 weeks, and the effect sustained throughout to 48 weeks. The medical officer also concluded that Evkeeza appeared to be effective in three pediatric patients.

The serious risks associated with Evkeeza during clinical trials were serious hypersensitivity reactions and embryo-fetal toxicity. These risks will be communicated in the Warnings and Precautions section of the labeling if the product is approved. Evkeeza will likely be prescribed by lipid specialists and pediatric lipid specialists who are familiar with these risks and how to manage them.

Patients with HoFH have markedly elevated LDL-C and rarely meet their target LDL-C, even with multiple lipid-lowering medications, including lomitapide. Lomitapide was approved by the FDA in 2012 as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce LDL-C in patients with HoFM. The safety issues associated with lomitapide include high rates of gastrointestinal side effects and hepatotoxicity. Lomitapide was approved with a REMS with ETASU to ensure the benefits outweigh the potential risk of hepatotoxicity. Patients with HoFH could potentially benefit from lipid apheresis, but many patients do not receive it due to the lack of a qualified lipoprotein apheresis centers, the burden of weekly or every 2 weeks apheresis sessions, and costs associated with

the treatment. There still exists an unmet clinical need for new therapies that reduce LDL-C and the risk for premature ASCVD for patients with HoFM. Evkeeza provides a therapeutic option for patients with HoFH with a reasonable safety profile.

9 CONCLUSION & RECOMMENDATIONS

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for Evkeeza to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 APPENDICES

10.1 REFERENCES

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[4] Baigent C, Keech A, et al; Cholesterol treatment trialists (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in14 randomized trials of statins. *Lancet.* 2005; 366: 1267-1278.

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[8] Juxtapid (Lomitapide) REMS, rems@fda, accessed 12/08/2020

[9] Lipoprotein Apheresis Centers, thefhfoundation.org/diagnosis-management/treatment-for-hofh/lipoprotein-apheresis-centers, accessed 12/08/2020

[10] Evkeeza BLA 761181 draft prescribing information, accessed 12/17/2020

[11] Higginbotham, L. Evinacumab (Evkeeza) BLA 761181 Mid-cycle meeting, 09/09/2020

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