

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125559Orig1s000

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

**Department of Health and Human Services
Public Health Service
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 (REMS) Review

Date: July 20, 2015

Reviewer(s): Amarilys Vega, M.D., M.P.H, Medical Officer
Division of Risk Management (DRISK)

Team Leader: Naomi Redd, Pharm.D., Acting Team leader, DRISK

Division Director: Cynthia LaCivita, Pharm.D., Acting Director, DRISK

Drug Name(s): Alirocumab (Praluent[®])

OND Review Division: Division of Metabolism and Endocrinology Products

Therapeutic Class: Human monoclonal antibody (mAb), proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor

Dosage and Route: 75 mg or 150 mg administered subcutaneously once every 2 weeks

Application Type/Number: BLA 125559

Submission Number: Seq. No. 0000 (1)

Applicant/sponsor: Sanofi-aventis U.S. LLC

OSE RCM #: 2014-2425

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that should not be released to the public.**

1 INTRODUCTION

This review documents the Division of Risk Management's (DRISK) evaluation of whether a risk evaluation and mitigation strategy (REMS) is necessary for alirocumab (BLA 125559, received by FDA on November 24, 2014), a new molecular entity.

Sanofi-aventis proposes that alirocumab be indicated as an adjunct to diet, for long-term treatment of adult patients with primary hypercholesterolemia (non-familial and heterozygous familial) or mixed dyslipidemia including patients with type 2 diabetes mellitus, to reduce LDL-C, Total-C, non-HDL-C, Apo B, TG, and Lp(a), and to increase HDL-C and Apo A-1 either in combination with a statin or as monotherapy including in patients who cannot tolerate statins

The sponsor did not submit a REMS or a Risk Management Plan with this application; instead, the sponsor submitted a document including the rationale for not submitting a REMS. The review of alirocumab is classified as priority based on the use of a rare pediatric disease priority review voucher. The proprietary name Praluent received conditional approval on December 17, 2014.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Alirocumab BLA Introduction, Clinical Overview, Summary of Efficacy, Summary of Safety, Justification for Not Submitting a REMS and meeting correspondence history received by FDA on November 24, 2014.
- Alirocumab mid-cycle review meeting slides February 25, 2015.
- Alirocumab mid-cycle review communication letter April 10, 2015.
- Alirocumab draft product label, accessed version in SharePoint on April 15, 2015.
- Draft Alirocumab Clinical Review, Julie Golden, M.D. (efficacy) and Mary Roberts, M.D. (safety), accessed in SharePoint on July 20, 2015.

3 REGULATORY HISTORY

The regulatory history of alirocumab, pertinent to this review, is as follows:

- **November 24, 201:** FDA receives BLA 125559.
- **December 17, 2014:** FDA grants conditional approval for proprietary name Praluent.
- **February 25, 2015:** Mid-cycle review meeting
- **April 10, 2015:** Mid-cycle review communication letter issued. FDA reviewers reported no major efficacy or safety issues.
- **May 11, 2015:** Late cycle meeting
- **June 9, 2015:** Advisory Committee meeting
- **August 11, 2015:** Prescription Drug User Fee Act (PDUFA) action date

4 ASSESSMENT OF NEED FOR A REMS

4.1 RATIONALE FOR DRUG DEVELOPMENT^{1,2,3}

Atherosclerotic cardiovascular disease is the leading cause of death and disability in the Western world. Heart disease is the leading cause of death for both men and women in the United States (US). One in every 4 deaths in the US is due to heart disease – that is about 610,000 Americans each year. About 370,000 people die of coronary heart disease annually. In the US, the cost of coronary heart disease \$108.9 billion each year (cost of health care services, medications, and lost productivity).

Hypercholesterolemia, specifically increased low-density lipoprotein cholesterol (LDL-C), is a risk factor for the development of atherosclerotic cardiovascular disease. About 31% of adults in the US have high LDL-C (~73.5 million adults). Fewer than 1 out of every 3 adults (29.5%) of those with high LDL-C has the condition under control. Less than half (48.1%) of adults with high LDL-C are getting treatment to lower their LDL-C levels. Numerous studies have demonstrated that reduction of LDL-C levels results in reduction of cardiovascular disease.

Statins reduce LDL-C levels through inhibition of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase. Approximately 47 million patients had a prescription claim for HMG-CoA reductase inhibitors in 2013.⁴ However, some patients treated with statins cannot attain the reduction in LDL-C recommended in clinical guidelines and require additional treatment with other lipid-modifying therapies (e.g., ezetimibe, nicotinic acid, bile acid sequestrants, fibrates, and high-dose omega-3 fatty acids). Serious safety concerns associated to the use of statins include rhabdomyolysis, biochemical abnormalities of liver function, CNS hemorrhage, and increases in HbA1c and fasting serum glucose levels. There is a medical need for new safe and effective treatments for hypercholesterolemic patients, particularly for patients who cannot achieve control with the highest tolerated doses of statins or who do not tolerate statin-induced adverse effects.

Sanofi-aventis proposes that alirocumab be indicated for long-term treatment of adult patients with primary hypercholesterolemia (non-familial and heterozygous familial) or mixed dyslipidemia, including patients with type 2 diabetes mellitus, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (Total-C), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (Apo B), triglycerides (TG), and lipoprotein (a) [Lp(a)], and to increase high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A1 (Apo A-1). The proposed indication includes combination therapy with a statin (HMG-CoA reductase inhibitor), with or without other lipid-modifying therapy (LMT) or as monotherapy, or as add-on to other non-statin LMT, including in patients who cannot tolerate statins.

Alirocumab is a human monoclonal antibody with a high affinity and specificity for proprotein convertase subtilisin kexin type 9 (PCSK9). Low-density lipoprotein receptor (LDLR) is the primary receptor that clears circulating LDL-C. PCSK9 binds to the LDLR on the surface of hepatocytes and promotes LDLR degradation within the liver. Alirocumab increases the number of LDLRs available to clear LDL-C by inhibiting the binding of PCSK9 to LDLR, which results in reduction of LDL-C levels in the blood. Other PCSK9 inhibitors include evolocumab

¹ Alirocumab Clinical Overview, page 9

² Heart Disease Fact Sheet, CDC website at

http://www.cdc.gov/dhds/data_statistics/fact_sheets/fs_heart_disease.htm, accessed April 15, 2015.

³ High Cholesterol Facts, CDC website at <http://www.cdc.gov/cholesterol/facts.htm>, accessed April 16, 2015.

⁴ Justin Mathew, Pharm.D, Drug Use Data Analyst, Division of Epidemiology II, market review of Fenofibrates, Gemfibrozil, Choline Fenofibrate, dated August 11, 2014.

Alirocumab is formulated as a solution for subcutaneous injection. The recommended dose is 75 mg or 150 mg administered subcutaneously once every 2 weeks. Alirocumab comes as a 75 mg/mL or 150 mg/mL solution in a single-use pre-filled pen and as a 75 mg/mL or 150 mg/mL solution in a single-use pre-filled syringe. The pre-filled pens and pre-filled syringes are to be packaged in cartons containing one (1), two (2), ^{(b) (4)} one mL pre-filled pen(s) or pre-filled syringe(s) for the 75 mg and 150 mg doses. Alirocumab is intended for outpatient use.

4.2 CLINICAL DEVELOPMENT PROGRAM⁵

The clinical development program for alirocumab assessed its efficacy and safety in the treatment of patients with primary hypercholesterolemia or mixed dyslipidemia, as combination therapy with a statin, with or without other LMTs, or as monotherapy or add-on to non-statin LMTs, including in patients with statin intolerance. The main population in the phase 3 program consisted of patients with heterozygous familial hypercholesterolemia (HeFH) and non-familial hypercholesterolemia (non-FH) at high risk of atherosclerotic cardiovascular disease. The clinical development included: 11 clinical pharmacology studies; 7 phase 2 studies; 17 phase 3 studies (5 completed double-blind studies; 9 ongoing double-blind studies, and 3 ongoing open-label studies).

4.2.1 Efficacy

The integrated efficacy database included 10 phase 3 studies and 4 completed phase 2 studies. Phase 3 trials included 3 studies of HeFH patients, 5 of patients with cardiovascular risks with and without HeFH, 1 study of patients with intolerance to statin therapy, and 1 study of monotherapy in patients with moderate cardiovascular risk. Five of the 10 phase 3 trials were placebo-controlled and the remaining 5 were ezetimibe-controlled studies. The primary endpoint of these 10 studies was the percent change in LDL-C at 24 weeks.

In all studies, alirocumab demonstrated statistically significant LDL-C reductions. When pooling studies according to comparator and the presence/absence of background statin therapy, the LS mean reduction in LDL-C from baseline to Week 24 with alirocumab ranged from -45.6% to -48.9% with 75/150 mg every 2 weeks, and was -60.4% with 150 mg every 2 weeks. Superiority of alirocumab versus placebo was demonstrated as add-on to a statin in all placebo-controlled studies. In addition, superiority in LDL-C reduction was also demonstrated in ezetimibe-controlled studies, with alirocumab being administered as add-on to statin, or to LMTs other than statin, or in monotherapy, including in patients with a history of statin intolerance.

Division of Metabolism and Endocrinology Products (DMEP) concluded that treatment with alirocumab resulted in substantial and persistent LDL-C lowering than the controls; however, the impact of these finding on cardiovascular safety cannot be determined with the data available. The company is conducting an event-driven cardiovascular outcomes trial initiated in 2012 with an estimated enrollment of 18,000 patients with acute coronary syndrome. The objective of this trial is to establish the effect of alirocumab on cardiovascular morbidity and mortality.

⁵ Alirocumab Clinical Overview, Sanofi.

4.2.2 Safety

The integrated safety database includes the same 10 phase 3 studies, as well as the four completed phase 2 studies included in the integrated efficacy database. There were two main safety pools included in the analysis: (1) placebo-controlled pool (9 trials – 4 phase 2 trials and 5 phase 3 trials) as an add-on to statin therapy, (2) ezetimibe-controlled pool (5 phase 3 trials, with and without statin therapy). The integrated safety pool included a total of 5234 patients with hypercholesterolemia of which 3340 patients were treated with alirocumab at a dose of 75 or 150 mg administered SC every 2 weeks.

There was no difference in the safety profile observed between the 2 doses (75 mg and 150 mg). Adverse events of special interest (AESI) included local injection site reactions, general allergic events, neurologic events including neurocognitive events, skeletal muscle-related AEs, diabetes mellitus, ALT increase and ophthalmologic events. The percentages of patients experiencing at least 1 treatment emergent adverse event (TEAE), treatment-emergent serious adverse events (SAE) or TEAEs leading to permanent treatment discontinuation were similar between the alirocumab and placebo groups and between the alirocumab and ezetimibe groups. The percentage of deaths was observed in the alirocumab group was lower than that observed in either of the comparator groups. Injection site reactions, pruritus and influenza are TEAEs that were identified as adverse drug reactions. Injection site reactions and general allergic events (mostly due to pruritus) are AESI identified as potentially related to alirocumab; however, no relationship was found for neurologic events, neurocognitive events, other AESI, or diabetes.

DMEP determined that many of the safety concerns raised during the review process appear to lend themselves to monitoring and/or are manageable with labeling and pharmacovigilance. Key safety concerns identified by the Agency include: (1) increased incidence of shift to worse glycemic category, (2) hypersensitivity reactions, and (3) increased incidence of liver enzyme abnormalities. The proportion of patients meeting the criteria for the diabetes category diagnosed either by adverse event or laboratory value was 3.2% in the alirocumab group and 2.2% in the placebo group. The incidence of new onset diabetes mellitus with alirocumab treatment will be further investigated as a post-marketing requirement.⁶

4.3 ANTICIPATED CLINICAL USE

If approved for all the indications proposed by alirocumab's sponsor, the anticipated patient and prescriber populations for alirocumab will overlap with those of the statins. Therefore, the anticipated patient population for alirocumab is likely to include millions of patients and the anticipated prescriber population will likely include primary care physicians as well as specialists.

Due to the chronic nature of the disease being treated, alirocumab will likely be used for long periods of time or until the end of life.

4.4 ADVISORY COMMITTEE RECOMMENDATIONS

On June 9, 2015 members of the Endocrine and Metabolic Drugs Advisory Committee (EMDAC) voted 13:3 to the question, "Has the applicant sufficiently established that the LDL-

⁶ Draft Alirocumab Clinical Review, Julie Golden, M.D. (efficacy) and Mary Roberts, M.D. (safety), accessed in SharePoint on July 20, 2015.

C-lowering benefit of alirocumab exceeds its risks to support approval in one or more patient populations (excluding HoFH)?” Six panel members suggested the approved indication should be limited to patients with Familial Hypercholesterolemia. The remaining 7 panel members supported a broader indication including patients at high risk of cardiovascular events and/or those who cannot tolerate statins. In the absence of outcomes data, panel members expressed their uncertainty about the reliability of LDL-C reduction to serve as a surrogate for clinical benefit with non-statin drugs. In addition, some panel members expressed their concern that approval of alirocumab could jeopardize the completion of the ongoing outcomes trial.

4.5 OVERALL BENEFIT:RISK ASSESSMENT

DMEP determined that the clinical development program for alirocumab demonstrated a favorable benefit:risk balance for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease who require additional lowering of LDL-C.⁷

4.6 RECOMMENDED RISK MANAGEMENT APPROACH

The sponsor submitted a document including the rationale for why a REMS is not required for alirocumab. In summary, the sponsor proposed managing the risks associated with alirocumab through labeling. (b) (4)

[REDACTED]

[REDACTED] (b) (4)

Based on the available data, the seriousness of key safety concerns associated with the use of alirocumab identified by DMEP (i.e., increased incidence of shift to worse glycemic category, hypersensitivity reactions, and increased incidence of liver enzyme abnormalities) do not rise to a level that would require a box warning or additional measures beyond labeling and routine pharmacovigilance. Therefore, DRISK does not recommend a REMS to manage the risks associated with alirocumab.

5 CONCLUSION AND RECOMMENDATIONS

The clinical development program for alirocumab demonstrated that the use of this drug results in substantial and persistent LDL-C lowering than the controls. The frequency and severity of the key safety concerns identified for this product (i.e., increased incidence of shift to worse glycemic category, hypersensitivity reactions, and increased incidence of liver enzyme abnormalities) do not warrant management measures beyond labeling and routine pharmacovigilance. DRISK and DMEP agree that a REMS is not needed to manage the risks associated with alirocumab.

Please keep DRISK informed if new safety information becomes available that would necessitate this benefit: risk profile to be re-evaluated.

⁷ Draft Product Label July 6, 2015.

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/s/

AMARILYS VEGA
07/20/2015

CYNTHIA L LACIVITA
07/20/2015
Concur