



BLA 125559

**BLA APPROVAL**

Sanofi-Aventis U.S. Inc.  
Attention: Jana Bodorova, M.Sc.  
Senior Director, Global Regulatory Affairs  
55 Corporate Drive, Mail Stop: 55D-215A  
Bridgewater, NJ 08807

Dear Ms. Bodorova:

Please refer to your Biologics License Application (BLA) dated and received November 24, 2014, submitted under section 351(a) of the Public Health Service Act for Praluent (alirocumab) injection, 75 mg and 150 mg.

We acknowledge receipt of your amendments dated December 17 and 19, 2014, and January 12, 13, 20 and 27, February 13 (3), 20 (2), and 25, March 4, 9, 11 (2), 17, 18, 20, 23, 25, 26, and 30, April 1, 6, 7, 8, 10 (2), 14, 16 (2), 17 (2), 20 (2), 22, 23, 24, 27, 29, and 30, May 8 (3), 11, 18, 22 (2), 26 (2), and 27, June 1, 5, 18, 23, 29, and 30, and July 2 (2), 6, 9, 22, and 23 (2), 2015.

**LICENSING**

We have approved your BLA for Praluent (alirocumab) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Praluent, under your existing Department of Health and Human Services U.S. License No. 1752. Praluent is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C.

**MANUFACTURING LOCATIONS**

Under this license, you are approved to do the following:

1. Manufacture Praluent drug substance in (b) (4)
2. Manufacture final formulated drug product in bulk pre-filled syringes, and label and package pre-filled syringes at Sanofi Winthrop Industrie, 1051 Boulevard Industriel 76580, Le Trait, France.

3. Assemble bulk pre-filled syringes [REDACTED] (b) (4) and label and package pre-filled pens at Sanofi-Aventis Deutschland GmbH, Bruningstrabe 50, Industriepark Höchst, 65926 Frankfurt am Main, Germany.
4. Perform secondary packaging for distribution at Sanofi-Aventis U.S. LCC, 6239-6244 Lemay Ferry Roda, Saint Louis, MO or at Sanofi-Aventis Deutschland GmbH, Bruningstrabe 50, Industriepark Höchst, 65926 Frankfurt am Main, Germany.
5. Label your product with the proprietary name, Praluent, and market it in single-dose, pre-filled syringes and pens containing 75 mg/mL or 150 mg/mL solution for subcutaneous injection.

### **DATING PERIOD**

The dating period for Praluent shall be 18 months from the date of manufacture when stored at 2°C to 8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored [REDACTED] (b) (4)

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

### **FDA LOT RELEASE**

You are not currently required to submit samples of future lots of Praluent to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Praluent, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

### **APPROVAL & LABELING**

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, and text for the instructions for use). Information on submitting SPL

files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

### **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)”. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved BLA 125559.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for pediatric patients with clinical atherosclerotic cardiovascular disease because studies would be impossible or highly impractical as this condition rarely occurs in pediatric patients.

We are waiving the pediatric study requirement for patients with heterozygous familial hypercholesterolemia (HeFH) ages 0 through 9 years (inclusive) because studies would be impossible or highly impractical because the standard of care, which is highly effective, is based on diet and lifestyle modification.

We are deferring submission of your pediatric studies for patients with HeFH ages 10 to 17 years (inclusive) for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must

be reported annually according to 21 CFR 601.28 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

2927-1 Conduct a dose-finding study (Phase 2) and an efficacy and safety study (Phase 3) evaluating alirocumab in patients with heterozygous familial hypercholesterolemia (HeFH) ages 10 years to less than 18 years. If children younger than age 10 are included, the eligibility criteria should ensure that other available interventions to lower LDL-C have been insufficient. Phase 2 will be a randomized, open-label, 8-week, ascending repeated dose-finding study of alirocumab with an optional open-label extension study in patients 10 years to less than 18 years of age with HeFH on stable lipid modifying therapy with LDL-C  $\geq$  130 mg/dL. Phase 3 will be a randomized, 6-month, double-blind, placebo-controlled, parallel-group, multicenter efficacy and safety study followed by an 18-month open-label extension in patients 10 years to less than 18 years with HeFH on stable lipid-modifying therapy with LDL-C  $\geq$  130 mg/dL. Patients treated in Phase 2, the dose-finding study, will be offered enrollment in Phase 3, the efficacy and safety study.

Final Protocol Submission (Phase 2):	January 2016
Final Protocol Submission (Phase 3):	December 2017
Study Completion (Phase 2):	December 2018
Study Completion (Phase 3):	April 2022
Final Report Submission (Phase 2 and 3):	September 2022

Submit the protocols to your IND 105574, with a cross-reference letter to this BLA.

Reports of these required pediatric postmarketing studies must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of adverse fetal, infant, and childhood outcomes related to humoral immune suppression with Praluent.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 2927-2 Conduct a prospective observational study of pregnant women exposed to Praluent to evaluate fetal, infant, and childhood outcomes of pregnant women exposed to Praluent and their live born offspring through the first 5 years of life to estimate incidence rates for the potential safety signals of adverse pregnancy outcomes, embryo-fetal growth and development, and adverse infant and childhood outcomes related to humoral immune suppression. The study should have validated/adjudicated outcomes, a comparator group, be powered to detect the outcomes of interest, and include the justification for the proposed detectable differences in incidence rates.

The timetable you submitted on July 20, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	July 2016
Interim Report Submissions:	July 2017
	July 2018
	July 2019
	July 2020
	July 2021
	July 2022
	July 2023
	July 2024
	July 2025
	July 2026
	July 2027
	July 2028
	July 2029
Study Completion:	June 2030
Final Report Submission:	December 2030

Finally, we have determined that only clinical trials (rather than a nonclinical or observational study) will be sufficient to:

- Assess a signal of serious risks of new-onset diabetes mellitus, injection site reactions, hypersensitivity, and immunogenicity with Praluent
- Identify an unexpected serious risk of changes in neurocognitive function with Praluent

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 2927-3 Conduct a large, randomized, controlled, long-term trial in which the incidence and severity of new-onset diabetes mellitus, injection site reactions, hypersensitivity, immunogenicity, and adverse events potentially related to demyelination with alirocumab treatment will be evaluated.

The timetable you submitted on July 20, 2015, states that you will conduct this trial according to the following schedule:

Final Analysis Plan Submission:	January 2016
Trial Completion:	March 2018
Final Report Submission:	August 2018

- 2927-4 Conduct a randomized, controlled, long-term trial that prospectively evaluates changes in neurocognitive function with alirocumab treatment. The trial must be adequately powered to exclude a clinically meaningful adverse effect.

The timetable you submitted on July 20, 2015, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	February 2016
Trial Completion:	August 2020
Final Report Submission:	December 2020

Submit the protocols to your IND 105574, with a cross-reference letter to this BLA. Submit all final reports to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

**POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitment:

- 2927-5 To develop an algorithm for decision-making in the presence of loss of efficacy due to antibody response. This should include an examination of the binding of alirocumab-specific neutralizing antibodies to the LDL receptor in patients in whom the presence of anti-drug antibodies are associated with LDL-C levels > 1.5-fold baseline in the absence of other confounding factors (e.g., non-adherence or intentional changes in concomitant LDL-C-lowering medications).

The timetable you submitted on July 20, 2015, states that you will conduct this study according to the following schedule:

Study Completion:	September 2018
Final Report Submission:	February 2019

**POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitments:

- 2927-6 Repeat the microbial retention study (b) (4)



The timetable you submitted on July 20, 2015, states that you will conduct this study according to the following schedule:

Study Completion:	December 2015
Final Report Submission:	February 2016

- 2927-7 Qualification of the bioburden and sterility test methods was performed with only two lots of drug product, with the exception of qualification of the sterility test method for the recovery of *A. brasiliensis*. As a post-marketing commitment, provide bioburden and sterility test qualification data from one additional batch of 150 mg/mL drug product that was not manufactured from drug substance batches 8065000001 or 8065000002. The study may be done with bulk drug product.

The timetable you submitted on July 20, 2015, states that you will conduct this study according to the following schedule:

Study Completion: May 2016  
Final Report Submission: September 2016

2927-8 [REDACTED] (b) (4)  
Revise the container closure integrity test method to include a system suitability control with [REDACTED] (b) (4).

The timetable you submitted on July 20, 2015, states that you will conduct this study according to the following schedule:

Study Completion: May 2016  
Final Report Submission: September 2016

2927-9 Implement [REDACTED] (b) (4)  
The hold time limits should be supported by the studies performed to fulfill PMC 10.

The timetable you submitted on July 20, 2015, states that you will conduct this study according to the following schedule:

Study Completion: March 2016  
Final Report Submission: May 2016

2927-10 To confirm that reduced endotoxin recovery over time is not observed with the [REDACTED] (b) (4)  
The study should be designed to support the proposed endotoxin testing [REDACTED] (b) (4)

The timetable you submitted on July 20, 2015, states that you will conduct this study according to the following schedule:

Study Completion: March 2016  
Final Report Submission: May 2016

2927-11 Revise the [REDACTED] (b) (4) bioburden limit for [REDACTED] (b) (4) after data from additional drug product batches has been analyzed.



The timetable you submitted on July 20, 2015, states that you will conduct this study according to the following schedule:

Study Completion:	May 2016
Final Report Submission:	September 2016

Submit clinical protocols to your IND 105574 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol,**” “**Postmarketing Commitment Final Report,**” or “**Postmarketing Commitment Correspondence.**”

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

### **REPORTING REQUIREMENTS**

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Compliance Risk Management and Surveillance  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Compliance Risk Management and Surveillance  
10903 New Hampshire Avenue, Bldg. 51, Room 4206  
Silver Spring, MD 20903

### **MEDWATCH-TO-MANUFACTURER PROGRAM**

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

### **POST APPROVAL FEEDBACK MEETING**

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from

improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

### **PDUFA V APPLICANT INTERVIEW**

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Patricia Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

*{See appended electronic signature page}*

Mary H. Parks, M.D.  
Deputy Director  
Office of Drug Evaluation II  
Office of New Drugs  
Center for Drug Evaluation and Research

#### ENCLOSURES:

- Content of Labeling
- Package Insert
- Patient Package Insert
- Instructions for Use
- Carton and Container Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARY H PARKS  
07/24/2015