



BLA 125522/Original 1

BLA APPROVAL

Amgen, Inc.
Attention: Marc Kubasak, PhD
Senior Manager, Regulatory Affairs
One Amgen Center Drive, Mail Stop 17-2-B
Thousand Oaks, CA 01320-1799

Dear Dr. Kubasak:

Please refer to your Biologics License Application (BLA) dated and received August 27, 2014, submitted under section 351(a) of the Public Health Service Act for Repatha (evolocumab) injection, 140 mg/mL.

We acknowledge receipt of your amendments dated September 16, 23, 24, and 29, October 10, 13, 22, 23, 27, 28, and 31, November 3, 5, 24 (2), December 11 and 16 (2), and 17, 2014, and January 8, 12, and 29, February 17, and 26 (2), March 2, 5 (2), 16 (2), 24, 25, 27, and 30, April 2, 3 (2), 8, 9, 20, 21, 23, 24 (2), and 27, May 5, 7 (2), 8, 13, 14, 18, and 22 (2), June 1, 3, 4 (2), 5(2), 8, 9, 10, 15, 17, 22, 24 (2), 26, July 8, 15, and 20, August 11, 14(2), 18, 25(5), and 26(3), 2015. We also acknowledge receipt of your email dated August 27, 2015, stating your agreement to the labeling revisions we communicated to you by email on August 27, 2015.

BLA 125522 provides for the use of Repatha (evolocumab) for the following indications which, for administrative purposes, we have designated as follows:

- BLA 125522/Original 1 - Repatha 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. Repatha is also indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C. This application only includes a 420 mg once monthly dosing regimen for the HoFH indication.

(b) (4)

The subject of this action letter is BLA 125522/Original 1. [REDACTED]

(b) (4)

LICENSING

We have approved your BLA for Repatha (evolocumab) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Repatha under your existing Department of Health and Human Services U.S. License No. 1080. Repatha 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. Repatha is also indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C. This application only includes a 420 mg once monthly dosing regimen for the HoFH indication.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture evolocumab drug substance [REDACTED]

(b) (4)

The final formulated prefilled syringe drug product will be manufactured at Amgen Inc. B20, Thousand Oaks, CA, and at Amgen Manufacturing Ltd, AML-1, Juncos, Puerto Rico.

The final formulated prefilled SureClick[®] autoinjector drug product will be manufactured at Amgen Manufacturing Ltd, AML-1, Juncos, Puerto Rico.

You may label your product with the proprietary name, Repatha, and will market it as a 1 mL single-use prefilled syringe containing 140 mg/mL evolocumab injection and as a 1 mL single-use SureClick[®] autoinjector containing 140 mg/mL evolocumab injection.

DATING PERIOD

The dating period for Repatha 140 mg prefilled syringe shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product.

The dating period for Repatha SureClick[®] 140 mg autoinjector shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The expiration date for the Repatha SureClick[®] autoinjector shall not exceed the shortest shelf life of any of the Repatha SureClick[®] autoinjector components.

The dating period for evolocumab formulated bulk drug substance shall be [REDACTED] months from the date of manufacture when stored at [REDACTED]°C.

(b)
(4)

Results of ongoing stability studies should be submitted to the annual report.

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 Repatha 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 Repatha, 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 125522/Original 1.**”

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.

(b) (4)

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.

Because this drug product has an orphan drug designation for the homozygous familial hypercholesterolemia (HoFH) indication, you are exempt from this requirement for that indication.

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 less than 18 years 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 (FDCA) 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 FDCA. These required studies are listed below.

- 2946-1 Conduct an efficacy and safety study evaluating Repatha (evolocumab) in patients with heterozygous familial hypercholesterolemia (HeFH) ages 10 years to less

than 18 years. The study will be a randomized, 6-month, double-blind, placebo-controlled, parallel-group, multicenter efficacy and safety study (Part A) 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 (Part B).

Final Protocol Submission (Part A):	December 2015
Final Protocol Submission (Part B):	December 2015
Study Completion (Part A):	March 2018
Study Completion (Part B):	September 2019
Final Report Submission (Parts A and B):	April 2020

Submit the protocols to your IND 105188, 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 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 Repatha.

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:

- 2946-2 Conduct a prospective observational study of pregnant women exposed to Repatha (evolocumab) to evaluate fetal, infant, and childhood outcomes of pregnant women exposed to evolocumab 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 August 14, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	August 2016
Interim Report Submissions:	October 2017
	October 2018
	October 2019
	October 2020
	October 2021
	October 2022
	October 2023
	October 2024
	October 2025
	October 2026
	October 2027
	October 2028
	October 2029
Study Completion:	October 2030
Final Report Submission:	April 2031

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 Repatha;
- Identity an unexpected serious risk of changes in neurocognitive function with Repatha.

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

- 2946-3 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 Repatha (evolocumab) will be evaluated.

The timetable you submitted on August 14, 2015, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	January 2016
Trial Completion:	September 2017
Final Report Submission:	June 2018

- 2946-4 Conduct a randomized, controlled, long-term trial that prospectively evaluates changes in neurocognitive function with Repatha (evolocumab) treatment. The

trial must be adequately powered to exclude a clinically meaningful adverse effect.

The timetable you submitted on August 14, 2015, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: November 2015
Trial Completion: September 2017
Final Report Submission: June 2018

Submit the protocols to your IND 105188, 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 NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2946-5 To establish the evolocumab drug substance (DS) stability acceptance criteria for the 9- and 12-month stability timepoints at the (b) (4) C condition based on available stability data.

The timetable you submitted on August 14, 2015, states that you will conduct this study according to the following schedule:

Study Completion: November 2016
Final Report Submission: December 2016

Acceptance criteria and supporting data should be submitted as a Changes Being Effected (CBE) supplement.

- 2946-6 To demonstrate that the identity by ELISA assay performed at Amgen Thousand Oaks (ATO) for evolocumab drug product (DP) lot release testing functions within the parameters identified for the validated assay prior to releasing evolocumab lots tested for identity at ATO.

The timetable you submitted on August 14, 2015, states that you will conduct this study according to the following schedule:

Study Completion: September 2015
Final Report Submission: December 2015

- 2946-7 To re-evaluate the evolocumab drug substance (b) (4) limits (b) (4). The final report should include the corresponding data, the analysis and statistical plan used to evaluate (b) (4) limits, and any proposed changes to the limits.

The timetable you submitted on August 14, 2015, states that you will conduct this study according to the following schedule:

Study Completion: March 2017
Final Report Submission: July 2017

- 2946-8 To re-evaluate the evolocumab DP acceptance criteria (b) (4) as specified in PMC 7. The DP lots will include the lots which were used in the analysis of specifications submitted in the BLA and subsequent drug product lots manufactured. The final report should include the corresponding data, the analysis and statistical plan used to evaluate the (b) (4) limits, and any proposed changes to the limits. The analysis should also include linkage to the drug substance (b) (4) limits (b) (4) based on the re-evaluation specified in PMC 7.

The timetable you submitted on August 14, 2015, states that you will conduct this study according to the following schedule:

Study Completion: March 2017
Final Report Submission: July 2017

- 2946-9 To re-evaluate the evolocumab drug product release and stability acceptance criteria for the prefilled syringe and autoinjector presentations after the manufacture of DP lots from an additional 2 DS manufacturing campaigns. The

final report should include the corresponding data, the analysis and statistical plan used to evaluate the results and acceptance criteria, and any proposed changes to the criteria.

The timetable you submitted on August 14, 2015, states that you will conduct this study according to the following schedule:

Study Completion:	March 2017
Final Report Submission:	July 2017

Submit clinical protocols to your IND 105188 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>.

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 Kati Johnson, Senior Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
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 (Autoinjector, Prefilled Syringe)
- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CURTIS J ROSEBRAUGH
08/27/2015