DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125320/S-186

**SUPPLEMENT APPROVAL**

Amgen Inc.
Attention: Rajas Chodankar, Ph.D.
Manager; Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-C
Thousand Oaks, CA 91320-1799

Dear Dr. Chodankar:

Please refer to your Supplemental Biologics License Application (sBLA), dated and received July 28, 2017, and your amendments, submitted under section 351(a) of the Public Health Service Act for Prolia (denosumab).

We also refer to our approval letter dated May 18, 2018, which contained the following errors:

- Omission of the postmarketing study information for the deferred pediatric study for ages 5 to 17 years
- Correction to lumbar spine bone mineral density percentages presented in Section 14.3 of the Prescribing Information

This replacement approval letter incorporates the correction of the errors. The effective approval date will remain May 18, 2018, the date of the original approval letter.

This Prior Approval supplemental biologics application provides for revisions to the Prescribing Information (PI) and Medication Guide to add a new indication for the treatment of osteoporosis associated with newly initiating or sustained systemic glucocorticoid therapy in men and women at high risk for fracture.

## APPROVAL & LABELING

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

## WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

## 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 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the prescribing information, text for the Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. 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.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

## REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 ages 0 to 4 years because there is evidence strongly suggesting that the drug product would be unsafe in this pediatric group because of the high rates of skeletal growth and the potential for Prolia to negatively affect long-bone growth and dentition.

We are deferring submission of your pediatric study for ages 5 to 17 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be

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

#3422-1 "A Phase 3 Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Safety and Efficacy of Denosumab in Pediatric Subjects With Glucocorticoid-induced Osteoporosis" (Study 20140444)

Study/Trial Completion: 12/2022
Final Report Submission: 09/2023

We acknowledge receipt of this protocol to your IND 009837 on September 29, 2017.

Reports of this required pediatric postmarketing study 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 the serious risks of serious infection including skin infection, dermatologic adverse events, or over-suppression of bone turnover (including atypical fractures, osteonecrosis of the jaw, and hypocalcemia).

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 studies:

#2399-2 A long-term observational study in administrative databases to prospectively evaluate the incidence of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover in postmenopausal women administered Prolia (denosumab). This postmarketing required study (PMR) is described in the June 1, 2010, approval letter for Prolia. PMR #2957-1 added the population of men to the same study in an efficacy approval letter dated, September 20, 2012.

The timetable you submitted on May 28, 2010, states that you will conduct this study according to the following schedule:

Study Completion Date: December 2022
Final Report Submission: June 2023

#2399-3 A long-term surveillance study in postmenopausal women administered Prolia (denosumab) to prospectively evaluate the incidence of serious infection including skin infections, dermatologic adverse events, and over-suppression of bone turnover. This PMR is described in the June 1, 2010, approval letter for Prolia. PMR #2957-1 added the population of men to the same study in an efficacy approval letter dated, September 20, 2012.

The timetable you submitted on May 28, 2010, states that you will conduct this study according to the following schedule:

Study Completion Date: December 2021
Final Report Submission: June 2022

#3396-1 Inclusion of a new target population, adults with glucocorticoid-induced osteoporosis (GIOP), in the required postmarketing study entitled, "The Denosumab Global Postmarketing Safety Observational Study" (Study 20090522), designated above as PMR 2399-#2 (or PMR #2).

Your submission on May 14, 2018, states that you will propose a sub-study in the GIOP population in Study 20090522 by May 28, 2018.

The timetable you submitted on May 28, 2010, states that you will conduct this study according to the following schedule:

Study Completion Date: December 2022
Final Report Submission: June 2023

#3396-2 Inclusion of a new target population, adults with glucocorticoid-induced osteoporosis, in the required postmarketing study entitled, "The Prolia Postmarketing Active Safety Surveillance Program" (Study 20090601), designated above as PMR 2399-#3 (or PMR #3).

Your submission on May 14, 2018, states that you will submit an amendment to include the GIOP population in Study 20090601 by May 28, 2018.

The timetable you submitted on May 28, 2010, states that you will conduct this study according to the following schedule:

Study Completion Date: December 2021

Final Report Submission: June 2022

Submit clinical protocol(s) to your IND 09837 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) 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).**

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

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.

## RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The evaluation of the continued need for this REMS is ongoing and will be conveyed in a separate communication.

## 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 prescribing information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf ).

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the prescribing information, 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**

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Samantha Bell, Regulatory Project Manager, at (301) 796-9687.

Sincerely,

*{See appended electronic signature page}*

Audrey Gassman, M.D.
Deputy Director
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Content of 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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AUDREY L GASSMAN
05/18/2018