DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125320/162

SUPPLEMENT APPROVAL

Amgen, Inc.
Attention: Julia Zhu, Pharm.D., R.A.C.
Senior Associate, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-1-C
Thousand Oaks, CA 91320-1799

Dear Dr. Zhu:

Please refer to your Supplemental Biologics License Application (sBLA), dated and received on May 29, 2014, submitted under section 351(a) of the Public Health Service Act for Prolia® (denosumab).

We acknowledge receipt of your amendments dated November 5, 2014, and January 28, April 3, and May 11, 2015.

We also refer to our REMS Modification Notification letter dated February 28, 2014.

This supplemental biologics application, as amended, provides for proposed modifications to the approved Prolia (denosumab) risk evaluation and mitigation strategy (REMS).

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter.

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 none of these criteria applies to your application, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Prolia® (denosumab) was originally approved on June 1, 2010, and REMS modifications were approved on September 16, 2011, May 10 and June 7, 2012, September 20, 2012, July 3, 2013, June 16, 2014, and last modified on February 26, 2015. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

In order to ensure the benefits of Prolia® (denosumab) outweigh its risks, we determined that you were required to make the following REMS modifications:

1. Changes to the REMS goal statement

2. Changes to the Communication Plan

   - Replacement of the Dear Healthcare Provider letter with a REMS Letter for Healthcare Providers and a REMS Letter for Professional Societies

   - Addition of a Patient Counseling Toolkit which contains a Patient Counseling Tool for Healthcare Providers, a Patient Brochure, and copies of the product labeling and Medication Guide

   - Addition of a Journal Information Piece

   - Dissemination of Prolia REMS-related information at scientific Meetings

   - Changes to the Prolia REMS website to reflect the aforementioned modifications

3. Changes to the timetable for submission of REMS assessments (see below).

Your proposed modified REMS, submitted on May 29, 2015, and appended to this letter, is approved.

The modified REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the proposed modified REMS must be revised as follows:

> Amgen will submit REMS Assessments to FDA at 18 months, 3, 6, and 7 years from the date of the initial approval (June 1, 2010). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting

interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Amgen will submit each assessment so that it will be received by the FDA on or before the due date.

The revised REMS assessment plan should include, but is not limited to, the following:

1. An evaluation of the implementation of REMS Communication Plan activities:

    a. Launch date of revised communication plan

    b. Number of Healthcare Providers (HCPs) (stratified by specialty) and professional societies targeted by the REMS

    c. REMS Letters: A summary that includes the following information, reported both cumulatively and stratified by distribution waves (ie, date distributed):
        i. Purpose of distribution
        ii. Target audience for distribution
        iii. Total distribution number for REMS Letter for Healthcare Providers and REMS Letter for Professional Societies
        iv. Total hardcopy REMS Letter to Healthcare Providers communications mailed, returned, and resent after obtaining correct address
        v. Total REMS Professional Society email communications sent, undeliverable, opened, and returned for which a hard copy letter was mailed

    d. Number and specialty of prescribers who received the Patient Counseling Toolkit

    e. Date when the revised REMS website went live and number of unique site visits during the assessment period and cumulative

    f. Journal name and dates of information piece publication

    g. List of scientific meetings in which Prolia REMS information was made available

2. Evaluation of HCPs’ knowledge:

    a. An evaluation of HCPs' understanding of the serious risks of Prolia, including the risks of hypocalcemia, osteonecrosis of the jaw, atypical femoral fractures, serious infections, and dermatologic reactions via analysis of assessment survey results; and stratify results by HCP specialty (e.g., endocrinologist, rheumatologist, primary care provider)

b. An evaluation of HCPs' understanding of the need for counseling patients about the risks associated with Prolia therapy; and stratify results by HCP specialty

c. An evaluation of HCPs' understanding of the requirement to give each patient a copy Patient Brochure via analysis of assessment surveys results

3. Evaluation of patients' knowledge:

a. An evaluation of patients' understanding of the serious risks of Prolia (denosumab), including hypocalcemia, osteonecrosis of the jaw, atypical femoral fractures , serious infections, and dermatologic adverse reactions.

b. An evaluation of whether patients receive the Medication Guide when dispensed the drug and the Patient Brochure from their prescriber via analysis of assessment survey results.

4. Safety Surveillance:

a. Prolia utilization information including but not limited to indication and type of HCP (i.e., endocrinologist, general practitioner, internist, etc.)

b. A summary and analysis of all postmarketing case reports of hypocalcemia, osteonecrosis of the jaw, atypical femoral fractures, serious infections, and dermatologic reactions with analysis stratified by HCP specialty

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any of goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A). This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that the last assessment and if any modifications of the REMS have been proposed since that assessment.
e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125320 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

BLA 125320 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 125320/SECONDARY TRACKING NUMBER CHANGES BEING EFFECTED IN 30 DAYS
< other supplement identification >
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 125320/SECONDARY TRACKING NUMBER
PRIOR APPROVAL SUPPLEMENT
< other supplement identification >
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 125320/SECONDARY TRACKING NUMBER
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125320/SECONDARY TRACKING NUMBER
REMS ASSESSMENT
< other supplement identification >
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR BLA 125320

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

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 Meredith Alpert, MS, Safety Regulatory Project Manager, at (301) 796-1218.

Sincerely,

{See appended electronic signature page}

Christine P. Nguyen, MD
Deputy Director for Safety
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
REMS

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

/s/

CHRISTINE P NGUYEN
05/21/2015