



BLA 125320/150

SUPPLEMENT APPROVAL

Amgen, Inc.
Attention: Judy Vong
Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop 38-4-C
Thousand Oaks, CA 91320-1799

Dear Ms. Vong:

Please refer to your Supplemental Biologics License Application (sBLA), dated November 5, 2013, and received November 6, 2013, submitted under section 351(a) of the Public Health Service Act for Prolia® (denosumab).

We acknowledge receipt of your amendments dated March 28, May 8 and 22, June 4 and 12, 2014, and your risk evaluation and mitigation strategy (REMS) assessment dated November 5, 2013.

We also refer to our safety labeling change (SLC) notification letters dated February 28 and April 8 and 29, 2014, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for Prolia. This information includes the following:

- 1) reports of severe musculoskeletal pain associated with the use of Prolia
- 2) findings of the second (3-year) REMS assessment, which require re-ordering of the risks in the Warnings and Precautions sections of the Prescribing Information (PI) and Medication Guide (MG) to better reflect the relative clinical importance of these warnings.
- 3) postmarketing reports of marked elevations in serum parathyroid hormone (PTH) levels, in patients with severe renal impairment or receiving dialysis, associated with Prolia use.

This supplemental biologics application provides for revisions to the labeling for Prolia, consistent with our February 28, and April 8 and 29, 2014, letters. These agreed upon changes include:

- Addition of a new Warning of Musculoskeletal Pain

- Revision to the existing Warning of Calcium and Mineral Metabolism to include marked elevations of serum parathyroid hormone seen in patients with several renal impairment, and
- The re-ordering of risks in Warnings and Precautions.

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.

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 package insert, Medication Guide and include the labeling changes proposed in any pending “Changes Being Effectuated” (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 includes labeling changes for this BLA, including pending “Changes Being Effectuated” (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.

We request that the labeling approved today be available on your website within 10 days of receipt 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 apply 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, and last modified on July 3, 2013. The REMS consists of a Medication Guide, communication plan, and a timetable for submission of assessments of the REMS. Your proposed modification to the REMS consist of a revised Medication Guide reflecting the re-ordering of the risks in Warnings and Precautions and the addition of a new warning of severe musculoskeletal pain.

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.

The timetable for submission of assessments of the REMS will remain the same as that approved on June 1, 2010.

There are no changes to the REMS assessment plan described in our June 1, 2010, letter.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

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 the 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
PROPOSED REMS MODIFICATION**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125320
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

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

PROMOTIONAL MATERIALS

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), 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>.

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4) to the address above or by fax to 301-847-8444.

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

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(S):
Content of Labeling
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
06/16/2014