



BLA 125320/78

**SUPPLEMENT APPROVAL**

Amgen, Inc.  
Attention: Tammy Rose  
Senior Manager, Regulatory Affairs  
One Amgen Center Drive  
Mail Stop 17-2-B  
Thousand Oaks, CA 91320-1799

Dear Ms. Rose:

Please refer to your Supplemental Biologics License Application (sBLA), dated and received April 20, 2012, submitted under section 351 of the Public Health Service Act for Prolia® (denosumab).

We acknowledge receipt of your amendments dated May 29, and June 4, 2012; and your risk evaluation and mitigation strategy (REMS) assessment dated June 4, 2012.

This “Prior Approval” labeling supplement to your biologics license application provides for the following changes to the Prolia Dear Health Care Provider (DHCP) letter and modifications to the REMS document.

- DHCP Letter: Revised to include the serious risks of hypocalcemia, inform providers of the REMS survey results, and increase the provider’s awareness of the importance of the Medication Guide.
- REMS Document: Revised goals to include the serious risk of hypocalcemia.

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 and the 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>. For administrative purposes, please designate this submission “**Product Correspondence – Final SPL for approved BLA STN 125320/78.**”

Also within 14 days, amend all pending supplemental applications 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.

The SPL will be accessible via publicly available labeling repositories.

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 was originally approved on June 1, 2010, and REMS modifications were approved on September 16, 2011 and May 10, 2012. The REMS consists of a Medication Guide, communication plan, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of changes to the REMS document goals and the DHCP letter to include the serious risks of hypocalcemia. The DHCP letter also contains proposed revisions to increase provider’s awareness of the importance of the Medication Guide, and inform the providers of the survey results.

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.

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  
REMS ASSESSMENT**

**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**

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(s) 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(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. 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 Meredith Alpert, Regulatory Project Manager, at (301) 796-1218.

Sincerely,

*{See appended electronic signature page}*

Christine Nguyen, M.D.  
Acting Deputy Director for Safety  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

ENCLOSURES:  
Content of Labeling  
REMS

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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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CHRISTINE P NGUYEN  
06/07/2012