



BLA 125320/S-181

**SUPPLEMENT APPROVAL**

Amgen Inc.  
Attention: Julia Zhu, Pharm.D., RAC  
Manager, Regulatory Affairs  
One Amgen Center Drive, Mail Stop 17-1-C  
Thousand Oaks, CA 91320

Dear Dr. Zhu:

Please refer to your Supplemental Biologics License Application (sBLA), dated and received July 29, 2016, and your amendments, submitted under section 351(a) of the Public Health Service Act for Prolia<sup>®</sup> (denosumab) injection, 60 mg/1 mL solution in a prefilled syringe, and Xgeva<sup>®</sup> (denosumab) injection, 120 mg/1.7 mL (70 mg/mL) solution in a vial.

This Prior Approval supplemental biologics application provides for:

- Manufacturing and testing of denosumab drug substance (DS) at Amgen Singapore (ASM) manufacturing facility (b)(4)
- Testing of (b)(4) denosumab DS, including introduction of new test methods, at Amgen Manufacturing, Limited (AML) facility
- Manufacturing and testing of denosumab drug products (DP) manufactured (b)(4) at AML facility
- Testing of denosumab DPs manufactured (b)(4) at Amgen Technology Ireland (ADL) facility
- Revisions to the Dosage and Administration, Dosage Form and Strength, Description, and How Supplied/Storage and Handling sections of the Prolia Prescribing Information (PI) to remove references to the denosumab 60 mg vial (60 mg/ml) vial (b)(4)
- Revisions to Description section of the Xgeva PI to add 0.01% polysorbate 20 to the DP formulation
- Revision to the Xgeva carton and container labeling to add 0.01% polysorbate 20
- Revisions to the Xgeva and Prolia PI to comply with Pregnancy and Lactation Labeling Rule (PLLR) format

## **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, 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.

## **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels **and** carton and immediate container labels submitted on July 29, 2016, 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 — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission “**Product Correspondence – Final Printed Carton and Container Labels for approved BLA 125320/ S-181.**” Approval of this submission by FDA is not required before the labeling is used.

### **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.

### **POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitments:

3216-1 To provide confirmatory data by executing (b) (4) commercial runs (b) (4)  
(b) (4) The process parameters, (b) (4)  
(b) (4) will be recorded. The final report, containing the process parameters, in-process controls (IPC) data, and (b) (4) profiles, will be submitted on February 28, 2019, as an Annual Report for the reporting period ending on December 31, 2018.

The timetable you submitted on May 8, 2017, states that you will conduct this study according to the following schedule:

Study Completion: October 2018  
Final Report Submission: February 2019

3216-2 To provide additional assurance that the master cell bank (MCB) is (b) (4)  
(b) (4) Amgen will characterize (b) (4)

The timetable you submitted on May 10, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: June 2018

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**.”

### **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}*

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

### ENCLOSURES:

Content of Labeling  
Carton and Container 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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CHRISTINE P NGUYEN  
05/26/2017