DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125320/7

SUPPLEMENT BLA APPROVAL
November, 18, 2010

Amgen, Incorporated
Attention: John Bergan
Senior Manager, Regulatory Affairs and Safety
One Amgen Center Drive
Mail Stop 38-4C
Thousand Oaks, CA 91320-9978

Dear Mr. Bergan:

Please refer to your Supplemental Biologics License Application (sBLA), dated May 14, 2010, received May 19, 2010, submitted under section 351 of the Public Health Service Act for denosumab.

We acknowledge receipt of your amendments dated May 14, 2010, July 23, 2010 (2), July 28, 2010, July 29, 2010, August 5, 2010, August 16, 2010, August 23, 2010 (2), August 24, 2010 (2), August 31, 2010, September 7, 2010, September 10, 2010, September 22, 2010, October 11, 2010, October 22, 2010, October 27, 2010 (4), October 28, 2010 (2), October 29, 2010, November 11, 2010, November 15, 2010, and November 18, 2010.

This "Prior Approval" efficacy supplement to your BLA provides for a new indication to include the prevention of skeletal-related events in patients with bone metastases from solid tumors to be marketed under a new proprietary name, Xgeva. 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 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/U

CM072392.pdf. For administrative purposes, please designate this submission "**Product Correspondence – Final SPL for approved BLA STN 125320/7**."
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.

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels 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 – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved BLA STN 125320/7**." 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric studies because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 601.28 and section 505B (a)(3)(B) of the FDCA. These required studies are listed below.

1. To conduct a phase 1, open-label, dose-finding pharmacokinetic, pharmacodynamic, and safety study in pediatric patients ages 0 to 18 years who are diagnosed with solid tumors metastatic to bone. The study will determine whether a safe dose can be administered to patients in subsequent phase 2 and phase 3 studies.

   The timetable you submitted on October 29, 2010 states that you will conduct this study according to the following schedule.

   Final Protocol Submission: December 30, 2011

Study Completion Date: March 31, 2014
Final Report Completion: September 30, 2014

2. To conduct a phase 2, open-label, single-arm study in pediatric patients ages 0 to 18 with solid tumors with bone metastases to determine the safety, including effects on growing bones, and activity of denosumab in the prevention of skeletal related events.

   The timetable you submitted on October 29, 2010 states that you will conduct this study according to the following schedule.

   This study must not be initiated until at least one month after you have submitted the complete final report for postmarketing requirement 1.

   Final Protocol Submission: September 30, 2014
   Study Completion Date: September 30, 2018
   Final Report Submission: March 31, 2019

3. To conduct a randomized and controlled pediatric study to evaluate the efficacy and safety of denosumab for the prevention of skeletal related events in pediatric patients ages 0 to 18 years with solid tumors and bone metastases.

   This study must not be initiated until at least one month after you have submitted the complete final report for post marketing requirements 1 and 2.

   The timetable you submitted on October 29, 2010 states that you will conduct this study according to the following schedule.

   Final Protocol Submission: March 31, 2019
   Study Completion Date: March 31, 2025
   Final Report Submission: September 30, 2025

Submit final reports to this BLA. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated "**Required Pediatric Assessment(s)**."

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the 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.

Since denosumab was approved on June 1, 2010, we have become aware of the increased risk of severe hypocalcemia in patients with renal insufficiency from the clinical trial data submitted for approval of this application using the 120 mg dose of denosumab. Therefore, we consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

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 identify an unexpected serious risk of hypocalcemia in patients with severe renal insufficiency.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA is not yet sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of hypocalcemia in patients with severe renal insufficiency

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

4. To conduct a clinical trial to determine the safety of Xgeva (denosumab) 120 mg administered every four weeks by subcutaneous injection in patients with severe renal insufficiency (creatinine clearance less than 30 mL/min) and in patients receiving dialysis. The number of patients enrolled in the trial and the frequency and duration of plasma sampling will be sufficient to estimate the incidence and severity of hypocalcemia, hypomagnesemia, and hypophoshatemia in this patient population. The final report should include the primary and derived datasets using the CDISC and ADaM data models and the analysis programs used to generate the safety and laboratory analyses.

   The timetable you submitted on October 29, 2010 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	March 31, 2011
Trial Completion Date:	June 30, 2012
Final Report Submission:	December 31, 2012

Submit the protocol to your IND 9838, with a cross-reference letter to this BLA. Submit 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)"**.

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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment in your submission dated October 29, 2010. This commitment is listed below.

5. To submit a final report that includes updated results for overall survival for trials 20050103 entitled "A Randomized, Double-Blind, Multicenter Study of Denosumab Compared with Zoledronic Acid (Zometa®) in the Treatment of Bone Metastases in Men with Hormone-Refractory Prostate Cancer;" 200050136 entitled "A Randomized, Double-blind, Multicenter Study of Denosumab Compared With Zoledronic Acid (Zometa) in the Treatment of Bone Metastases in Subjects With Advanced Breast Cancer;" and 20050244 entitled "A Randomized, Double-Blind, Multicenter Study of Denosumab Compared With Zoledronic Acid (Zometa) in the Treatment of Bone Metastases in Subjects With Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma." The final report should also include the primary and derived datasets and analysis programs used to generate the overall survival results reported.

   The original protocol for clinical trial 20050103 was submitted to FDA on January 12, 2006, and began patient accrual on May 12, 2006. The original protocol for clinical trial 20050136 was submitted to FDA on January, 13, 2006, and began patient accrual on April 27, 2007. The original protocol for clinical trial 20050244 was submitted to FDA on May 2, 2006, and began patient accrual on June 21, 2006.

   The timetable you submitted on October 07, 2010 states that you will conduct the trials according to the following schedule:

   Final Report Submission: October 01, 2012.

Submit clinical protocols to your IND 9838 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all 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**."

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
Division of Drug Marketing, Advertising, and Communications
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 Division of Drug Marketing, Advertising, and Communications (DDMAC), 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 Melanie Pierce, Senior Regulatory Health Project Manager, at (301) 796-1273.

Sincerely,

/ Patricia Keegan, M.D./
Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling