DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125320/94

SUPPLEMENT APPROVAL

Amgen, Incorporated
Attn: Thomas M. DeMelfi, Jr., M.S.
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. DeMelfi:

Please refer to your Supplemental Biologics License Application (sBLA), dated December 11, 2012, received December 12, 2012, submitted under section 351(a) of the Public Health Service Act for Xgeva (denosumab).

We acknowledge receipt of your amendments dated December 11, 2012, January 16, 2013, January 25, 2013, February 4, 2013, February 26, 2013, March 8, 2013, March 11, 2013, March 19, 2013, May 13, 2013, May 23, 2013, May 31, 2013, June 7, 1013, June 10, 2013 and June 12, 2013.

This 'Prior Approval" supplemental to your BLA provides for a new indication for the treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity. 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/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 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.

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 this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (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 Xgeva (denosumab) was approved on November 18, 2010, we have become aware of risks (further described below) associated with long term use of Xgeva (denosumab) in adolescent and adult patients with giant cell tumor of bone (GCTB) from the clinical trial used to support the indication in GCTB. 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 longer duration of exposure to Xgeva (denosumab), and to assess signals of a serious risk of malignant transformation of GCTB with Xgeva (denosumab), secondary malignancies with Xgeva (denosumab), and embryo-fetal toxicity with Xgeva (denosumab), and to assess the known serious risk of osteonecrosis of the jaw with Xgeva (denosumab) and atypical fractures with Xgeva (denosumab).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess an unexpected serious risk of longer duration of exposure to Xgeva (denosumab); to assess signals of a serious risk of malignant transformation of GCTB with Xgeva (denosumab), secondary malignancies with Xgeva (denosumab), and embryo-fetal

toxicity with Xgeva (denosumab); and to assess the known serious risk of osteonecrosis of the jaw with Xgeva (denosumab) and atypical fractures with Xgeva (denosumab).

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

1. Submit a final report of follow-up safety data of Xgeva (denosumab) in patients with giant cell tumor of bone enrolled in the ongoing single arm trial through November 2012 for a minimum of five years or until death or lost to follow-up, whichever comes first. Comprehensively collect information regarding survival status, disease progression, serious adverse events, and adverse events of special interest including osteonecrosis of the jaw, pregnancy-related complications, atypical fractures, malignant transformation of giant cell tumor of bone, and secondary malignancies. Perform descriptive analyses of these safety data, including a subset analysis comparing the long-term safety of denosumab in adolescent and adult patients.

   The timetable you submitted on June 5, 2013, states that you will conduct this trial according to the following schedule:

   Final Report Submission: December 2019

Submit the protocol(s) to your IND 113617, 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 commitments:

2. Submit the final report including primary datasets, derived datasets, and analysis programs used to generate the safety and efficacy results for the ongoing single arm multicenter trial of denosumab in patients with giant cell tumor of bone. Include an analysis of radiographic response as determined by the local investigator in evaluable patients who received at least one dose of denosumab and underwent at least one post-baseline Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) tumor assessment during the trial. The primary analysis should be conducted after patients enrolled through November 2012 have had the opportunity to complete 12 months of treatment.

   The timetable you submitted on June 5, 2013, states that you will conduct this trial according to the following schedule:

   Final Report Submission: December 2019

3. Provide a detailed and thoughtful analysis of the risk factors associated with malignant transformation of GCTB and development of new sarcoma and the lifetime and annual incidences of these events in denosumab naïve patients. For this analysis, use data from a minimum of two representative databases in addition to information from published literature. Include subset analyses based on specific risk factors identified from the comprehensive investigation.

   The timetable you submitted on June 5, 2013, states that you will conduct this study according to the following schedule:

   Final Report Submission: December 2018

Submit clinical protocols to your IND 113617 for this product. 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**."

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.

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.

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) 795-1273.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, MD
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

PATRICIA KEEGAN
06/13/2013