CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125320

OTHER ACTION LETTER(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125320/0
BL 125331/0

COMPLETE RESPONSE
October 16, 2009

AMGEN, Inc.
Attention: Edward S. Burd, Ph.D.
Senior Director, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-B
Thousand Oaks, CA 91320-9978

Dear Dr. Burd:

Please refer to your biologics license applications, dated December 19, 2008, received December 19, 2008, submitted under section 351 of the Public Health Service Act for Prolia (denosumab), for the treatment and prevention of osteoporosis in postmenopausal women.

We acknowledge receipt of your amendments dated January 13, 15, 20, 22, and 28, February 12 and 27, March 3, 5, 9, 12, 11, 13, and 18, April 6, 17, 15, 23, 29, and 30, May 1, 4, 15, 19, and 27, June 5, 9, 12, and 25, July 10, 13, and 20, August 7, 18, 26 (2), and 31, and September 3, 10, 11, 18, and 28, 2009.

We also acknowledge receipt of your amendments dated October 8 and 12, 2009, which were not reviewed for this action. You may incorporate applicable sections of the amendments by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of your applications, as amended, and have determined that we cannot approve these applications in their present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

Regarding the proposed indication for **treatment of postmenopausal osteoporosis** (under BLA 125320):

Clinical Deficiency

1. We have reviewed your proposed postmarketing observational study [Protocol 20090522 (Phase B): *"Denosumab Global Safety Assessment Among Women With Postmenopausal Osteoporosis (PMO) Using Multiple Observational Databases"*]. Because of the design and methodological challenges noted in your proposal, there is concern that the proposed study will not successfully capture the necessary safety information regarding denosumab use.

Therefore, additional assessment of methodology and background adverse event rates as specified under Protocol 20090521 (Phase A) is needed before agreement can be reached on the design of Protocol 20090522 (Phase B).

Information Needed to Address the Clinical Deficiency

It is necessary for you to complete your methodology and background adverse event rate assessment study [Protocol 20090521 (Phase A): *"Denosumab Global Safety Methodology and Background (AE) Rate Assessment Among Women With Postmenopausal Osteoporosis (PMO) Using Multiple Observational Databases"*] and submit the data for review prior to approval.

Regarding the proposed indication for **prevention of postmenopausal osteoporosis** (under BLA 125331):

RISK EVALUATION AND MITIGATION STRATEGIES (REMS) REQUIREMENTS

3. As described in our letter dated October 2, 2009, in accordance with section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA), we have determined that a REMS is necessary for Prolia (denosumab) to ensure that the benefits of the drug outweigh the risks of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover. We have determined that under section 505-1, the REMS for this product must include a Medication Guide, a communication plan, and a timetable for submission of assessments.

   We acknowledge the submission of your proposed REMS on October 8, 2009. Once FDA finds the content of your REMS acceptable and determines that BLA 125320 can be

approved, we will append the REMS, Medication Guide, and all relevant REMS materials including educational and communication materials to the approval letter. If and when BLA 125320 is approved, BLA 125331 will be converted to a supplement of BLA 125320.

LABELING

4. We reserve comment on the proposed labeling until the applications are otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

POSTMARKETING REQUIREMENTS

As described in our letter dated October 2, 2009, FDA has determined that, if BLA 125320 is approved, you will be required to conduct post-marketing studies of Prolia (denosumab) to assess the signal of a serious risk of serious infection, including skin infections, dermatologic adverse events, and over-suppression of bone turnover. Specifically, we have determined that, if BLA 125320 is approved, you will be required, pursuant to section 505(o)(3) of the FDCA, to conduct the following:

1. A long-term observational study in administrative databases to prospectively evaluate the incidence of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover in postmenopausal women administered denosumab (Protocol 20090522)

2. A long-term surveillance study in postmenopausal women administered denosumab to prospectively evaluate the incidence of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover (Protocol 20090601)

3. A long-term pregnancy exposure registry study in denosumab users who become pregnant on the drug (Protocol 20090589)

We acknowledge receipt of your amendments dated September 11 and October 12, 2009 containing your proposed postmarketing studies to address these issues.

We will continue discussion of your postmarketing study proposals so that your complete response to this action letter contains adequately designed and acceptable studies. Comments regarding your protocols will be provided separately.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the initial submission.

   - Present tabulations of the new safety data combined with the initial data.

   - Include tables that compare frequencies of adverse events in the initial data with the retabulated frequencies described in the bullet above.

   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the initial data.

6. Provide updated exposure information for the clinical trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or withdraw the applications. If you do not take any of these actions, we will consider your lack of response a request to withdraw the applications under 21 CFR 601.3(c). A resubmission must fully address all the deficiencies listed, and will start a new review cycle. A partial response to this letter may not be reviewed and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the applications can be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, call the Regulatory Project Manager, Celia Peacock, R.D., M.P.H., at (301) 796-4154.

Sincerely,
Julie Beitz MD 10-16-09
/Julie Beitz/
Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research