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RESEARCH**

APPLICATION NUMBER:

761062Orig1s000

OTHER ACTION LETTERS



BLA 761062

COMPLETE RESPONSE

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 Biologics License Application (BLA) dated and received July 19, 2016, and your amendments, submitted under section 351(a) of the Public Health Service Act for romosozumab.

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

DEFICIENCY:

Preliminary findings from Study 20110142 show a higher incidence of cardiovascular serious adverse events with romosozumab compared to alendronate in women with postmenopausal osteoporosis. A similar signal was seen in Study 20110174, a smaller study comparing romosozumab to placebo in men with osteoporosis. These findings raise concerns that romosozumab may increase cardiovascular risk. Although Study 20070337 did not appear to have a cardiovascular safety signal, these disparate findings across studies require detailed review once the completed final analyses have been submitted. These additional data, including the efficacy data from the head-to-head comparison of romosozumab to alendronate, are needed before we can complete the benefit/risk assessment and determine whether the benefits of romosozumab outweigh its risks.

TO ADDRESS THIS DEFICIENCY:

Complete analyses of Studies 20110142 and 20110174. Submit the individual clinical study reports together with an integrated assessment of cardiovascular risk that takes into account the totality of the data. This should include the basis for your conclusion that the benefits of romosozumab outweigh the identified cardiovascular risks. Provide all pertinent narratives and datasets. We recommend that you request a meeting to discuss the details of your proposal for responding to the deficiency before you resubmit the application.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. 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/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

PROPRIETARY NAME

Please refer to correspondence dated, October 18, 2016, which addresses the proposed proprietary name, Evenity. This name was found acceptable pending approval of the application in the current review cycle. Resubmit the proposed proprietary name when you respond to the application deficiency.

SAFETY UPDATE

When you respond to the above deficiency, include a safety update. The safety update should include data from all nonclinical and clinical studies/trials of the product 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/clinical trials for the proposed indication using the same format as in the original submission.
 - Present tabulations of the new safety data combined with the original application data.
 - Include tables that compare frequencies of adverse events in the original application 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 trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial 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 original application data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this product. Include an updated estimate of use for product marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

On January 13, 2017, FDA issued a final guidance entitled “Nonproprietary Naming of Biological Products,” which states that FDA intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning for certain biological products. Your 351(a) BLA is within the scope of this guidance. FDA intends to assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

Please note this guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act (PRA) of 1995. These provisions of the guidance describe the submission of proposed suffixes to FDA and a sponsor’s related analysis of proposed suffixes, which are considered, under the PRA, as information collection. FDA is not currently implementing information collection provisions of the guidance.

However, provisions of the final guidance that do not describe the information collection provisions should be considered final and represent FDA’s current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b)). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission 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 application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," March 2015 at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Samantha Bell, Regulatory Project Manager, at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

JULIE G BEITZ
07/13/2017