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RESEARCH**

APPLICATION NUMBER:

208325Orig1s000

OTHER ACTION LETTERS



NDA 208325

COMPLETE RESPONSE

KAI Pharmaceuticals, Inc. a wholly owned subsidiary of Amgen, Inc.
Attention: Jennifer Steinbock, MA, RAC
Senior Manager, Regulatory Affairs
One Amgen Center Drive; Mail Stop: 17-2-A
Thousand Oaks, CA 91320-1799

Dear Ms. Steinbock:

Please refer to your New Drug Application (NDA) dated and received August 24, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for etelcalcetide injection.

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.

CLINICAL:

Deficiency

(b) (4)

We have determined that Study 20120360 does not provide the substantial evidence necessary to establish and support a claim that etelcalcetide will have superior efficacy compared to cinacalcet in the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis for the following reasons:

- a. The comparison compared the two products at less than the maximally recommended doses and cinacalcet dosing was suboptimal. Relative to the maximally recommended dose for each respective product, the starting dose and the dose increments with each escalation step was lower for cinacalcet. Relative to etelcalcetide, the number of steps required to reach the maximally recommended dose were more numerous in the cinacalcet arm. The time allowed for dose optimization was limited to 17 weeks and, over this 17 week period, etelcalcetide dosing was unfairly advantaged (i.e., higher relative starting dose, higher relative dose increments per dose escalation steps and fewer dose steps needed to reach the maximally recommended dose). We note that in the care setting dose optimization is not limited to a 17 week period. At trial end, average etelcalcetide doses were higher than cinacalcet doses (relative to each product's respective maximally recommended dose) and a greater proportion of etelcalcetide treated subject achieved a maximally recommended dose. At Week 17 and Week 21 a

greater proportion of patients in the cinacalcet arm required a dose increase suggesting these patients were not optimized during the 17 week titration phase or at the efficacy assessment phase and demonstrating that the dosing regimen used for dose optimization were not equivalent and favored etelcalcetide.

- b. No differences in tolerability (i.e., dose limiting toxicity) to explain the suboptimal cinacalcet dosing were identified in review of the data from Study 20120360. In fact, less subjects randomized to cinacalcet experienced the dose-limiting adverse reaction of hypocalcemia (i.e., suggests worse tolerability of etelcalcetide in the trial).
- c. The claim is based on a single, short-term, study comparing the effect of two drugs on a surrogate endpoint.
- d. The observed difference between treatments is small and unlikely to represent a clinically meaningful difference. We note that a 12% difference in response rate between groups at the end of six months was not considered clinically important when the non-inferiority margin for this study was selected.

To address this deficiency, you will need to [REDACTED] (b) (4) or carry out a second head-to-head study against cinacalcet which adequately addresses the dosing issues identified in the review of Study 20120360 and provides confirmatory evidence that etelcalcetide [REDACTED] (b) (4) in the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis.

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: 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

CARTON AND CONTAINER LABELING

Please resubmit draft carton and container labels that are identical to the carton and container labels submitted on August 15, 2016.

PROPRIETARY NAME

Please refer to correspondence dated, November 18, 2015 which addresses the proposed proprietary name, Parsabiv. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials 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/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 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.

POSTMARKETING REQUIREMENTS UNDER 505(o)(3)

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.

As discussed with you during review of your application, FDA has identified a signal of a serious risk of gastrointestinal bleeding in patients treated with etelcalcetide.

Based on the above, FDA has determined that if NDA 208325 is approved, an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of gastrointestinal bleeding.

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 this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that, if NDA 208325 is approved, you will be required to conduct the following:

Conduct a hypothesis-testing observational study to provide data regarding the potential association between etelcalcetide and fatal and non-fatal gastrointestinal bleeding. The study should have a comparator group, be powered to detect the outcomes of interest, with justification for the proposed detectable differences in incidence rates. Special attention should be given to complete data availability in dialysis patients with secondary hyperparathyroidism above and below the age of 65 years, the ability to ascertain cause of death in a timely manner, and a statistical consideration of competing risks. Secondary analyses should aim to quantify the exposure-risk window, including periods after exposure discontinuation. The choice of study design, data source(s), and sample size should be supported by a feasibility analysis submitted to and reviewed by FDA prior to protocol finalization.

Any additional specific details of this required postmarketing study, including a timetable and annual reporting requirements, will be described more fully in the approval letter for this application, if it is approved.

If you complete this study prior to re-submitting your application, you may include the final report and relevant data sets in your Complete Response submission to facilitate review of the information.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. 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 314.65. 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 FDA Guidance for Industry, "Formal Meetings Between FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

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

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Meghna M. Jairath, Pharm.D., Regulatory Project Manager, at (301) 796-4267.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Office Director
Office of Drug Evaluation II
Office of New Drugs
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/

CURTIS J ROSEBRAUGH
08/24/2016