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APPLICATION NUMBER:

204353Orig1s000

OTHER ACTION LETTERS



NDA 204353

COMPLETE RESPONSE

Janssen Pharmaceuticals Inc.
c/o Janssen Research & Development, LLC
Attention: Brandon D. Porter
Associate Director, Global Regulatory Affairs
3210 Merryfield Row
San Diego, CA 92121

Dear Mr. Porter:

Please refer to your New Drug Application (NDA) dated December 12, 2012, received December 12, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for canagliflozin and metformin hydrochloride tablets 50/500 mg, 150/500 mg, 50/1000 mg, and 150/1000 mg.

We acknowledge receipt of your amendments dated January 18, February 11, March 12, April 9, 26, and 30, May 3, June 27 and 28, August 13 and 15, September 18, and October 14, 2013.

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 / CLINICAL PHARMACOLOGY

1. The clinical and clinical pharmacology data submitted to support approval of the application are insufficient to allow reliance on the efficacy findings from NDA 204042, evaluating canagliflozin dosed once-daily, to support approval of the canagliflozin and metformin fixed dose combination product due to the following deficiencies.
 - a. Data supporting the existence of a robust relationship between plasma canagliflozin concentration and hemoglobin A1c (HbA1c) reduction is lacking. Specific deficiencies in the PK/PD model derived from NDA 204042 data were identified and communicated to you at the Mid and Late Cycle Meetings held on May 29, 2013 and September 12, 2013, respectively, and during a teleconference held on October 31, 2013. Refer to the minutes from the Mid and Late Cycle meetings, and the email dated October 30, 2013, for specifics. You have not satisfactorily resolved these deficiencies to date.

- b. Your Phase 1 study (DIA1032) is not sufficient to bridge efficacy findings between canagliflozin dosed once daily with canagliflozin dosed twice daily.



Delivering the daily dose in two administrations over a 24 hour period may impact the PD of canagliflozin.

- c. The bootstrap method to bridge findings between DIA2003 and DIA3006 cannot be used to address the above listed deficiencies. The information gained from this type of approach is exploratory as interpretation of the results are severely limited due to their post-hoc nature, reliance on non-randomized cross trial comparisons and adjustment made to only one of many potential differences between two studies (i.e., baseline glycemic control).

In order to address these deficiencies, you will need to bridge the efficacy of canagliflozin when the daily dose is administered once-daily to the efficacy of canagliflozin when the daily dose is administered twice-daily using a robust modeling and simulation strategy. We recommend you seek FDA guidance regarding model development. If you cannot generate a robust model with the data you have on hand, you will need to compare the efficacy of once-daily and twice-daily dosing of canagliflozin head to head in a clinical trial. This clinical trial should assess the change in HbA1c from baseline and the duration should be sufficient to allow the impact of canagliflozin on HbA1c change to be fully reflected (i.e., 12-16-weeks). We recommend you seek FDA guidance regarding the design and analysis plan prior to initiating this trial, if the modeling approach is not feasible.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, 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>.

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 the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA 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 NDA 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.

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. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference 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 the 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 Abolade (Bola) Adeolu, Regulatory Project Manager, at (301) 796-4264.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, MD
Director (Acting)
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
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/

JEAN-MARC P GUETTIER
12/11/2013