CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214408Orig1s000

OTHER ACTION LETTERS

NDA 214408

TENTATIVE APPROVAL

Accord Healthcare, Inc.
Attention: Sabita Nair, RAC, ASQ-CPGP
Vice President, Regulatory Affairs
1009 Slater Road, Suite 210-B
Durham, NC 27703

Dear Ms. Nair:

Please refer to your new drug application (NDA) dated and received January 27, 2020, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Pemetrexed Injection 100 mg/4 mL (25 mg/mL), 500 mg/20 mL (25 mg/mL), 850 mg/34 mL (25 mg/mL), and 1000 mg/40 mL (25 mg/mL).

We acknowledge receipt of your amendment dated November 17, 2021, which constituted a complete response to our November 23, 2020, action letter.

This NDA provides for the use of Pemetrexed Injection:

- in combination with pembrolizumab and platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.
- in combination with cisplatin for the initial treatment of patients with locally advanced or metastatic, non-squamous, NSCLC.
- as a single agent for the maintenance treatment of patients with locally advanced or metastatic, non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.
- as a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy.
- initial treatment, in combination with cisplatin, of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.

We have completed our review of this application, as amended. It is tentatively approved under 21 CFR 314.105 for use as recommended in the agreed-upon enclosed labeling (text for the Prescribing Information, Patient Package Insert, and carton and container labeling**)**. This determination is based upon information available to the Agency at this time, [i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product]. This determination is subject to change on the basis of any new information that may come to our attention.

Final approval of your application is subject to expiration of a period of patent protection and/or exclusivity. Therefore, final approval of your application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be granted before the period has expired.

To obtain final approval of this application, submit an amendment two or six months prior to the: (1) expiration of the patent(s) and/or exclusivity protection or (2) date you believe that your NDA will be eligible for final approval, as appropriate. In your cover letter, clearly identify your amendment as **"REQUEST FOR FINAL APPROVAL"**. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of any relevant court order or judgment settlement, or licensing agreement, as appropriate. In addition to a safety update, the amendment should also identify changes, if any, in the conditions under which your product was tentatively approved, i.e., updated labeling; chemistry, manufacturing, and controls data; and risk evaluation and mitigation strategy (REMS). If there are no changes, clearly state so in your cover letter. Any changes require our review before final approval and the goal date for our review will be set accordingly.

Until we issue a final approval letter, this NDA is not approved.

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

PROPRIETARY NAME

If you intend to have a proprietary name for this product, the name and its use in the labeling must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit a request for a proposed proprietary name review. (See the guidance for industry *Contents of a Complete Submission for the Evaluation of Proprietary Names*[1] and *PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022*.)

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that if this application is ultimately approved, you will need to meet these requirements.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have any questions, call Idara Ojofeitimi, Chief of Project Management Staff, at 301-796-3074.

Sincerely,

{See appended electronic signature page}

Harpreet Singh, M.D.
Director
Division of Oncology 2 (DO2)
Office of Oncologic Diseases (OOD)
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- Carton and Container Labeling

55 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIN A LARKINS
05/17/2022 06:26:11 PM

NDA 214408

COMPLETE RESPONSE

Accord Healthcare Inc.
Attention: Sabita Nair, RAC, ASQ-CPGP
Vice President, Regulatory Affairs
1009 Slater Road, Suite 210-B
Durham, NC 27703

Dear Ms. Nair:

Please refer to your new drug application (NDA) dated January 27, 2020, received January 27, 2020, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Pemetrexed Injection 100 mg/4 mL (25 mg/mL), 500 mg/20 mL (25 mg/mL), 850 mg/34 mL (25 mg/mL), and 1000 mg/40 mL (25 mg/mL).

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.

There is insufficient information provided to support the safety of the amount of the citric acid excipient in your proposed pemetrexed formulation in the context of the standard 10-minute infusion time for pemetrexed as there is published data suggesting that infusion of citric acid at rates that are close to the proposed rate can result in significant acute toxicity. Because this is a 505(b)(2) application that relies in part on FDA's previous findings of safety and efficacy for the listed drug and because there are multiple pemetrexed products that all use the same infusion rate, addressing the citric acid infusion rate through labeling is not a viable option to ensure patient safety.

NONCLINICAL

1. To address the identified safety issue, you may provide additional nonclinical safety data to show that infusion of the amount of citric acid present in your proposed formulation for Pemetrexed Injection is not acutely toxic. While we acknowledge the submission of a draft protocol of a nonclinical study intended to help address this safety issue, the study as currently designed does not appear sufficient to address this safety concern. Before you resubmit a nonclinical protocol to an IND for this acute animal toxicology study, we have the following high-level comments on the protocol:

a. In the study include a group without citric acid, a group with the proposed citric acid vehicle at a dose high enough to cover the proposed clinical dose, a group with Pemetrexed Injection at a dose high enough to cover the proposed clinical dose, and a group with the listed drug at a dose high enough to cover the clinical dose.

b. Include assessments of calcium levels in animals pre-infusion, immediately at the end of infusion, and 1 hour post infusion; other endpoints should include mortality, clinical observations, and, if possible cardiovascular effects; histopathological assessment is not necessary as the identified concern is an acute infusion-related toxicity.

c. Use a sufficient number of animals in each dosing group (at least 10 rodents/sex/group); recovery groups are not necessary.

d. A repeated-dose toxicology study is not necessary. The safety concern raised is specifically for acute toxic effects of citric acid infusion. A single dose toxicology study can address this concern.

PRODUCT QUALITY

2. The scientific bridge between the proposed Ready-To-Dilute Pemetrexed solution drug product and the relied upon Listed Drug product could not be established due to safety concerns related to the level of added citric acid in the proposed formulation. Adequate data/information to support the overall safety of the proposed drug product's ingredients should be provided in the NDA resubmission. Should the proposed drug product's formulation change, additional bridging data may be required.

PRESCRIBING INFORMATION

3. 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[1] and Pregnancy and Lactation Labeling Final Rule[2] 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.

[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

CARTON AND CONTAINER LABELING

4. Submit draft carton and container labeling.

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.

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

6. 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.

7. 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.

8. 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.

9. 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.

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

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

12. 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 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 guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

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 Idara Udoh, Senior Regulatory Health Project Manager, at 301-796-3074.

Sincerely,

{See appended electronic signature page}

Harpreet Singh, M.D.
Director
Division of Oncology 2 (DO2)
Office of Oncologic Diseases (OOD)
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

B HARPREET SINGH
11/23/2020 10:25:29 AM