CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215960Orig1s000

OTHER ACTION LETTERS

NDA 215960

COMPLETE RESPONSE

Spero Therapeutics, Inc.
Attention: Jennifer Liscouski-Cunningham
Vice President, Regulatory Affairs
675 Massachusetts Avenue, 14th Floor
Cambridge, MA 02139

Dear Ms. Liscouski-Cunningham:

Please refer to your new drug application (NDA) dated and received October 27, 2021, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tebipenem pivoxil tablets, 300 mg.

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/STATISTICAL

There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 21 CFR §314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling (21 CFR §314.125(b)(5)). The clinical data submitted from Study SPR994-301 do not provide substantial evidence of effectiveness of tebipenem pivoxil tablets for the proposed indication of treatment of complicated urinary tract infections (cUTI) in adult patients with limited oral treatment options. The reason for reaching this conclusion is that Study SPR994-301 failed to meet the pre-specified noninferiority criteria for the primary endpoint in the population of subjects with pathogens susceptible to the comparator drug.

To address this deficiency, we recommend you conduct an additional adequate and well-controlled trial or trials. If you conduct a single trial, it must be persuasive and accompanied by confirmatory evidence.

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

Prescription Drug Labeling Resources[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.

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated, January 12, 2022, which addresses the proposed proprietary name, (b) (4). 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 deficiency.

FACILITY INSPECTIONS

In addition to responding to the deficiency presented above, please note and acknowledge the following comment in your response. An inspection of the (b) (4) (b) (4), FEI# (b) (4), facility is required before this application can be approved. FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. Due to restrictions on travel, we were unable to complete an inspection during the current review cycle for your application. You may respond to the deficiency in this Complete Response Letter while the travel restrictions remain in effect. However, even if this deficiency is addressed, the application cannot be approved until the required FDA inspection is conducted and any findings are assessed with regard to your application. We will continue to monitor the public health situation as well as travel restrictions.

Because approval of your application requires an inspection that cannot be conducted in a timely manner due to COVID-19 travel restrictions, the FDA has made an initial determination that the amendment to your application in response to this complete response letter will be received as a Class 2 resubmission as described in the 2020 Guidance for Industry Review Timelines for Applicant Reponses to Complete Response Letters When a Facility Assessment Is Needed During the COVID-19 Public Health Emergency.

Please see the FDA's "An Update to the Resiliency Roadmap for FDA Inspectional Oversight" for more information on FDA's plan to resume inspections (https://www.fda.gov/media/154293/download). Also see the FDA guidances related to

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

COVID 19. These guidances can be found at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders.

SAFETY UPDATE

When you respond to the above deficiency, 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 subject 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.

ADDITIONAL COMMENTS

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

CLINICAL PHARMACOLOGY

We strongly recommend that you develop a bioanalytical assay that directly quantifies tebipenem concentrations in plasma for use in probability of target attainment (PTA) analysis. In order for PTA analysis to inform regulatory decision-making, the human plasma pharmacokinetic (PK) data used in this analysis should exhibit a high level of accuracy and precision. In this application, human tebipenem plasma PK data were not derived from a bioanalytical method specifically validated for determination of tebipenem concentrations in plasma and therefore, there are uncertainties surrounding the accuracy and precision of these data. Consequently, the results of PTA analysis informed by these data do not reliably provide confirmatory evidence of tebipenem's effectiveness or susceptibility test interpretive criteria (STIC).

NONCLINICAL/ PRODUCT QUALITY

An impurity (b) (4) was identified with a structural alert for mutagenicity unrelated to the pivoxil group in the prodrug. Additionally, the proposed limits are significantly higher than acceptable daily intake based on the Threshold of Toxicological Concern (TTC) as described in ICH Guidance M7(R1)[3]. The submission did not contain adequate data to evaluate the mutagenicity of (b) (4), as there was cytotoxicity in 3/5 bacterial strains in the 6-well mini-Ames assay, and one of the bacterial strains showed a positive result suggesting mutagenic potential. Further, the 6-well mini-Ames assay is not typically a preferred method to evaluate mutagenicity due to high variability in the data generated, particularly without adequate justification for its use. Additional nonclinical studies, including one or more in vitro mammalian mutagenicity assays (e.g., HPRT forward mutation assay, mouse lymphoma TK assay) or a single in vivo transgenic rodent assay, are recommended to further characterize the mutagenic potential of (b) (4).

CLINICAL

[3] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m7r1-assessment-and-control-dna-reactive-mutagenic-impurities-pharmaceuticals-limit-potential

Prior to initiating additional trials for a cUTI treatment indication, we recommend you conduct further evaluations of the activity of tebipenem pivoxil, with a particular focus on Enterobacterales, and proposed dosing for this indication. You may also consider evaluating the suitability of tebipenem pivoxil for other indication(s)/site(s) of infection with a different spectrum of causative pathogens.

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 Jacquelyn Rosenberger, PharmD, RAC, Senior Regulatory Project Manager, at (301) 796-9179.

Sincerely,

{See appended electronic signature page}

Adam Sherwat, MD
Deputy Director
Office of Infectious Diseases
Office of New Drugs
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/

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