



NDA 217556

COMPLETE RESPONSE

Venatorx Pharmaceuticals, Inc.
Attention: Chitrananda Abeygunawardana, PhD
Vice President, Regulatory Affairs
74 E. Swedesford Road, Suite 100
Malvern, PA 19355

Dear Dr. Abeygunawardana:

Please refer to your new drug application (NDA) (b) (4)

for cefepime for injection and taniborbactam for injection, co-packaged for intravenous use.

We also acknowledge receipt of your amendment dated (b) (4), which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

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.

PRODUCT QUALITY

(b) (4)

(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



NONCLINICAL

(b) (4)



(b) (4)

PRESCRIBING INFORMATION

(9) We acknowledge your (b) (4), response to our (b) (4), Labeling Discussion Comments for the Prescribing Information (PI), which was not reviewed for this action due to identified deficiencies that precluded further discussion of labeling. In your NDA resubmission, submit draft labeling that responds to our (b) (4), communication, incorporating your proposed (b) (4), edits.

Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.¹

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version and PDF version. The marked-up copy should include annotations that support any proposed changes.

Your proposed PI must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the Prescription Drug Labeling Resources² and Pregnancy and Lactation Labeling Final Rule³ websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

² <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>

³ <https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule>

of important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.
- Additional resources for the PI, patient labeling, and carton/container labeling.

CARTON AND CONTAINER LABELING

(10) We acknowledge receipt of your (b) (4), response to our (b) (4), Labeling Discussion Comments for carton and container labeling, which was not reviewed for this action due to identified deficiencies that precluded further discussion of labeling. In your NDA resubmission, submit draft labeling that responds to our (b) (4), communication, incorporating your proposed (b) (4), edits.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version and PDF version of the proposed revised container labels and carton labeling. The marked-up copy should include annotations that support any proposed changes.

PROPRIETARY NAME

(11) Please refer to the correspondence dated (b) (4) which addresses the proposed proprietary name, (b) (4). This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to all the application deficiencies that have been identified in this letter.

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 cefepime for injection and taniborbactam for injection, co-packaged for intravenous use 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 cefepime for injection and taniborbactam for injection, co-packaged for intravenous use. Include an updated estimate of use for cefepime for injection and taniborbactam for injection, co-packaged for intravenous use 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

1. Based on the review of new clinical pharmacology information submitted on (b) (4), we have determined that the proposed dosage of 1 g cefepime and 0.25 taniborbactam every 24 hours for patients on intermittent hemodialysis is expected to result in higher taniborbactam exposures compared to the exposures expected in all other patient populations. Therefore, the following supportive analyses are needed to identify a dosage for patients on intermittent hemodialysis that provides cefepime and taniborbactam exposures comparable to other patient populations and results in the probability of target

attainment of $\geq 90\%$:

- (1) Evaluate additional dosing regimens to address the potential for higher taniborbactam exposures.
- (2) Conduct probability of target attainment analysis using the latest updated population pharmacokinetic model.

We will send a follow-up information request detailing the specifics related to the aforementioned additional analyses.

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

If you have any questions, call

(b) (4)

Sincerely,

{See appended electronic signature page}

(b) (4)

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) (4)

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