CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213972Orig1s000

OTHER ACTION LETTERS

NDA 213972

COMPLETE RESPONSE

Iterum Therapeutics U.S. Ltd.
c/o Iterum Therapeutics Ltd. USA
Attention: Steven I. Aronin, M.D.
Senior Vice President and Head of Clinical Development
20 Research Parkway, Suite A
Old Saybrook, CT 06475

Dear Dr. Aronin:

Please refer to your new drug application (NDA) dated November 25, 2020, received November 25, 2020, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for sulopenem etzadroxil and probenecid tablets, 500 mg/500 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 and STATISTICAL

There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 21CFR §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 301 do not provide substantial evidence of effectiveness of sulopenem etzadroxil and probenecid tablets for the proposed indication of treatment of adult women with uncomplicated urinary tract infections (uUTI) caused by designated susceptible microorganisms proven or strongly suspected to be nonsusceptible to a quinolone. The reasons for reaching this conclusion are as follows:

1. Although statistical significance was demonstrated for the difference in overall response rate by treatment arm in the ciprofloxacin-resistant (mMITT-R) population, the results are not sufficient as a single trial without a second adequate and well-controlled trial.

2. The other trials conducted with sulopenem failed to meet their primary endpoint, and therefore, could not provide evidence of effectiveness. In addition, these negative trials call into question the effectiveness of sulopenem for the treatment of uUTI. In Study 301, significantly inferior results were observed in the overall response rate for

sulopenem compared to ciprofloxacin in the ciprofloxacin-susceptible (mMITT-S) population. Significantly inferior results for sulopenem were also observed in the complicated urinary tract infections trial (Study 302) and there was a lack of noninferiority of sulopenem in the complicated intra-abdominal infections trial (Study 303).

To address these deficiencies, we recommend you conduct at least one additional adequate and well-controlled study in uUTI and consider using a different active comparator drug in the study(ies) that is more reflective of currently recommended treatment for uUTI. Additionally, we recommend that you conduct further investigation to determine the optimal sulopenem dosing regimen for the proposed treatment indication(s) (see Additional Comments below).

We look forward to working with you on the design of the clinical trial(s) you plan to conduct to address the deficiencies noted above.

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.

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 FDA.gov.[3]

CONTAINER LABELS AND CARTON LABELING

Submit draft container labels and carton labeling revised as follows:

Container Labels and Carton Labeling

- To ensure consistency with the Prescribing Information, we recommend revising the recommended dosage statement, (b) (4) Prescribing Information" to read "Recommended Dosage: See prescribing information."

[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
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Container Labels

- Ensure that a linear barcode is included on the 10- and 30-count bottle labels in accordance with 21 CFR 201.25(c)(2). Additionally, we recommend that the container label linear barcode be oriented in a vertical position, as a barcode placed in a horizontal position may be difficult to scan due to the curvature of the bottle.

  Furthermore, when determining placement of the linear barcode, consider that the barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i).

- Ensure that a linear barcode is included on the blister cell. Additionally, when determining placement of the linear barcode, consider that the barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i).

Carton Labeling

- Add the linear barcode to your proposed (b) (4)-count unit-dose carton labeling. Additionally, when determining placement of the linear barcode, consider that the barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i).
- Ensure that the human-readable and machine-readable product identifier is included on each carton labeling. We recommend you include the intended location of the machine-readable (2D data matrix barcode) product identifier, near the human-readable portion of the product identifier information. For more information, see draft guidance, Product Identifiers Under the Drug Supply Chain Security Act.
- Additionally, we recommend you ensure there is sufficient white space between the linear barcode and 2-D matrix barcode to allow barcode scanners the ability to correctly read each barcode.

PROPRIETARY NAME

Please refer to correspondence dated, April 12, 2021, which addresses the proposed proprietary name, Orlynvah. 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.

ADDITIONAL COMMENTS

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

Results of the nonclinical PK/PD studies are inconclusive, therefore, there is insufficient evidence to support use of T>MIC as the PK/PD index that best describes sulopenem's therapeutic effect. There are several deficiencies in the analysis and interpretation of the dose-fractionation study results such as reliance on data from a single dosing schedule to delineate the relevant PK/PD index, and varying the models used in data fitting. Furthermore, there are significant concerns with the approach used for PK/PD target determination as outlined in the previous information request communications.

Therefore, we recommend that you conduct additional nonclinical PK/PD studies to better understand the PK/PD behavior of sulopenem and appropriately determine PK/PD targets to support dose selection for the proposed treatment indication(s). We encourage you to submit your study plans and protocols for our review before initiating these studies.

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 Christopher L. Smith, PharmD, Regulatory Project Manager, at (301) 796-4851.

Sincerely,

{See appended electronic signature page}

John Farley, MD, MPH
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/

JOHN J FARLEY
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