



NDA 212862

## LPAD PATHWAY APPROVAL

The Global Alliance for TB Drug Development, Inc. (TB Alliance)  
c/o Rho, Inc.  
Attention: David Shoemaker, PhD  
Senior Vice President, Research and Development  
2635 E NC Hwy 54  
Durham, NC 27713

Dear Dr. Shoemaker:

Please refer to your new drug application (NDA) dated and received December 14, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Pretomanid Tablets, 200 mg.

We also refer to your written request dated June 05, 2019 for approval under section 506(h) of the FDCA for the Limited Population Pathway for Antibacterial and Antifungal Drugs (the LPAD Pathway).

This new drug application provides for the use of Pretomanid Tablets as part of a combination regimen with bedaquiline and linezolid, for the treatment of adults with pulmonary extensively drug resistant (XDR), or treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis. Approval of this indication is based on limited clinical safety and efficacy data. This drug is indicated for use in a limited and specific population of patients.

### **APPROVAL & LABELING**

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

## **LPAD PATHWAY APPROVAL**

This application is furthermore approved under section 506(h) of the FDCA and marketing of this drug product is subject to the requirements for labeling and promotional materials described therein.

Under section 506(h)(7), FDA may terminate the limitations associated with the LPAD pathway when FDA has determined that the product is safe and effective for a broader population. The additional data supporting approval for the broader population should demonstrate the conditions of the LPAD pathway are no longer necessary for the drug product. If you decide to conduct clinical trials to support termination of limitations, submit final reports to this NDA as a supplemental application. For administrative purposes, designate this submission “**LPAD Pathway Termination Request.**”

## **WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS**

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

## **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.<sup>1</sup> Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*<sup>2</sup>

The SPL will be accessible via publicly available labeling repositories.

## **CARTON AND CONTAINER LABELING**

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD*

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

<sup>2</sup> 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>.

*Specifications.* For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 212862.**” Approval of this submission by FDA is not required before the labeling is used.

### **TROPICAL DISEASE PRIORITY REVIEW VOUCHER**

We also inform you that you have been granted a tropical disease priority review voucher, as provided under section 524 of the FDCA. This voucher entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. This priority review voucher may be transferred by you to another sponsor of a human drug or biologic application. When redeeming this priority review voucher, you should refer to this letter as an official record of the voucher. If the voucher is transferred, the sponsor to whom the voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the voucher was transferred. In addition, this priority review voucher has been assigned a tracking number, PRV NDA 212862. All correspondences related to this voucher should refer to this tracking number. For additional information regarding the priority review voucher see the guidance for industry *Tropical Disease Priority Review Vouchers*.

### **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*, 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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

**POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the serious risk of the development of antimicrobial resistance to pretomanid in *M. tuberculosis*. We have also determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess signals of the potential serious risks of male infertility, incorrect dosing in patients with renal or hepatic impairment, and carcinogenic potential.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

3682-1      Conduct a study to evaluate the effect of Pretomanid Tablets on human semen

The timetable you submitted on August 09, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 10/2019  
Study Completion:            09/2023  
Final Report Submission:    01/2024

3682-2      Conduct a global surveillance study for a five-year period after the introduction of Pretomanid Tablets to the market to monitor changes in *M. tuberculosis* susceptibility to pretomanid.

The timetable you submitted on August 09, 2019, states that you will conduct this study according to the following schedule:

Final protocol submission:        12/2019  
First interim report submission:    12/2021  
Second interim report submission: 12/2022  
Third interim report submission:    12/2023  
Fourth interim report submission: 12/2024

Study completion: 06/2025  
Final report submission: 12/2025

- 3682-3 Conduct a study to evaluate pharmacokinetics and safety of Pretomanid Tablets in subjects with renal impairment.

The timetable you submitted on August 09, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission: Submitted  
Study Completion: 06/2021  
Final Report Submission: 12/2021

- 3682-4 Conduct a study to evaluate pharmacokinetics and safety of Pretomanid Tablets in subjects with mild, moderate, and severe hepatic impairment.

The timetable you submitted on August 09, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission: Submitted  
Study Completion: 12/2020  
Final Report Submission: 06/2021

- 3682-5 Conduct a two-year rat carcinogenicity study with pretomanid.

The timetable you submitted on August 09, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission: Submitted  
Study Completion: 02/2020  
Final Report Submission: 08/2020

Finally, we have determined that only clinical trials (rather than a nonclinical or observational study) will be sufficient to assess the signal of the serious risk of hepatotoxicity.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

- 3682-6 Conduct the ZeNix trial to evaluate various doses and treatment durations of linezolid plus bedaquiline and Pretomanid Tablets for treatment of extensively drug-resistant pulmonary tuberculosis.

The timetable you submitted on August 09, 2019 states that you will conduct this trial according to the following schedule:

Final Protocol Submission: Submitted  
Trial Completion: 03/2023  
Final Report Submission: 07/2023

3682-7 Conduct the SimpliciTB trial to evaluate Pretomanid Tablets, bedaquiline, moxifloxacin, and pyrazinamide for treatment of drug-resistant pulmonary tuberculosis.

The timetable you submitted on August 09, 2019 states that you will conduct this trial according to the following schedule:

Final Protocol Submission: Submitted  
Trial Completion: 06/2023  
Final Report Submission: 10/2023

Submit clinical protocol(s) to your IND 69580 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

**Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

### **PROMOTIONAL MATERIALS**

Under section 506(h) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 356(h)), you are required to submit copies of all promotional materials, including promotional

labeling and advertisements, related to the drug subject to this marketing approval at least 30 calendar days prior to dissemination of the materials. You should submit your materials with a cover letter that clearly identifies the submission as a "Pre-Submission of Promotional Materials for a Limited Population Pathway Antibacterial or Antifungal Drug." If you have questions, you may contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200 and ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue. Please note that you are required to continue to comply with Agency regulation and submit all specimens of mailing pieces and any other labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement (21 CFR 314.81(b)(3)(i) and 21 CFR 601.12(f)(4)).

You may also seek advisory comment from the Agency on your promotional materials. Should you voluntarily choose to seek advisory comment, we ask that your submission include a separate, detailed cover letter that indicates you are seeking advisory comment together with three copies each of the promotional materials, annotated references, and approved package insert (PI), Medication Guide, and patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotions (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials and any requests for advisory comment electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

## **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

## **MEDWATCH-TO-MANUFACTURER PROGRAM**

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at [FDA.gov](http://FDA.gov).<sup>3</sup>

## **POST APPROVAL FEEDBACK MEETING**

New molecular entities and new biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Fariba Izadi, RPh, PharmD, Acting Safety Regulatory Project Manager, at 301-796-0563.

Sincerely,

*{See appended electronic signature page}*

John Farley MD, MPH  
Deputy Director  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

### ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling

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<sup>3</sup> <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>

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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.**  
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/s/  
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JOHN J FARLEY  
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