

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

213972Orig1s000

Trade Name: Orlynvah tablets

Generic or Proper Name: sulopenem etzadroxil and probenecid

Sponsor: Iterum Therapeutics US Limited

Approval Date: October 25, 2024

Indication: For the treatment of uncomplicated urinary tract infections (uUTI) caused by the designated microorganisms *Escherichia coli*, *Klebsiella pneumoniae*, or *Proteus mirabilis* in adult women who have limited or no alternative oral antibacterial treatment options.

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APPLICATION NUMBER:

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APPROVAL LETTER



NDA 213972

NDA APPROVAL

Iterum Therapeutics US Limited
Attention: Steven I. Aronin, MD
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 and received November 25, 2020, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Orlynvah (sulopenem etzadroxil and probenecid) tablets.

We acknowledge receipt of your amendment dated April 25, 2024, which constituted a complete response to our July 23, 2021, action letter.

This NDA provides for the use of Orlynvah (sulopenem etzadroxil and probenecid) tablets for the treatment of uncomplicated urinary tract infections (uUTI) caused by the designated microorganisms *Escherichia coli*, *Klebsiella pneumoniae*, or *Proteus mirabilis* in adult women who have limited or no alternative oral antibacterial treatment options.

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.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of the 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.¹ Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information) 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*.²

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 *SPL Standard for Content of Labeling Technical Qs & As*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 213972.**” Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Orlynvah (sulopenem etzadroxil and probenecid) tablets is 60 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room temperature].

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 are waiving the pediatric studies requirement for ages birth to less than 2 years because necessary studies are impossible or highly impracticable as most urinary tract infections in this age group are considered complicated.

We are deferring submission of your pediatric studies for ages 2 years to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

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

² 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>.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. These required studies are listed below.

- 4722-1 Conduct an open label, single-dose study to evaluate the pharmacokinetics, safety, and tolerability of sulopenem etzadroxil/probenecid in pediatric patients aged 12 years to less than 18 years with bacterial infection and receiving background antibacterial therapy.
- Draft Protocol Submission: 12/2024
Final Protocol Submission: 03/2025
Study Completion: 06/2026
Final Report Submission: 12/2026
- 4722-2 Conduct an open label, single-dose study to evaluate the pharmacokinetics, safety, and tolerability of sulopenem etzadroxil/probenecid in pediatric patients aged 2 years to less than 12 years with bacterial infection and receiving background antibacterial therapy.
- Draft Protocol Submission: 03/2027
Final Protocol Submission: 06/2027
Study Completion: 06/2029
Final Report Submission: 12/2029
- 4722-3 Conduct a randomized, controlled study to evaluate the safety, tolerability, and efficacy of sulopenem etzadroxil/probenecid in pediatric patients aged 2 years to less than 18 years with uncomplicated urinary tract infections (uUTI).
- Draft Protocol Submission: 12/2029
Final Protocol Submission: 03/2030
Study Completion: 06/2032
Final Report Submission: 12/2032

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.³

³ See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (October 2019).
<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

Submit the protocol(s) to your IND 129849, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

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 assess a signal of a serious risk of developing resistance to bacterial pathogens specific to the indication in the labeling.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

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

4722-4 Conduct a U.S. surveillance study over a five-year period after the introduction of sulopenem etzadroxil/probenecid to the market to determine if resistance or decreased susceptibility to sulopenem etzadroxil/probenecid is occurring in the target population of bacteria identified in the approved sulopenem etzadroxil/probenecid label.

The timetable you submitted on October 21, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	01/2025
Final Protocol Submission:	05/2025
Interim Report ⁴ :	08/2026
	08/2027
	08/2028
	08/2029
Study/Trial Completion:	06/2030
Final Report Submission:	08/2030

⁴ Interim or "other" milestones may include interim report submission or subject accrual milestones. Justification for these milestones should be described in Section D.3.

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.⁵

Submit clinical protocol(s) to your IND 129849 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(a)(1) 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(a)(1) 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

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs*.⁶

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication,

⁵ See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (October 2019).

<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁶ For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.⁷ Information and Instructions for completing the form can be found at FDA.gov.⁸

REPORTING REQUIREMENTS

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

POST APPROVAL FEEDBACK MEETING

New molecular entities 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.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website⁹.

⁷ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁸ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

⁹ <https://www.uspnf.com/>

If you have questions, call Sheel Shah, PharmD, Regulatory Project Manager, at 240-402-3968 or by email at Sheel.Shah@fda.hhs.gov.

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

ENCLOSURE(S):

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

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
10/25/2024 10:08:01 AM