CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

216483Orig1s000

Trade Name:	PIVYA tablets
Generic or Proper Name:	Pivmecillinam
Sponsor:	UTILITY therapeutics Ltd.
Approval Date:	April 24, 2024
Indication:	PIVYA is indicated for the treatment of female patients 18 years of age and older with uncomplicated urinary tract infections (uUTI) caused by susceptible isolates of *Escherichia coli*, *Proteus mirabilis*, and *Staphylococcus saprophyticus*.

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APPROVAL LETTER

NDA 216483

CORRECTED NDA APPROVAL

UTILITY therapeutics Ltd.
c/o Kleinfeld, Kaplan, and Becker
Attention: Daniel Dwyer
US Agent
1850 M Street, NW, Suite 800
Washington, DC 20036

Dear Daniel Dwyer:

Please refer to your new drug application (NDA) dated and received October 24, 2023, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Pivya (pivmecillinam) tablet.

We also refer to our approval letter dated April 24, 2024, which contained the following error: In the **REQUIRED PEDIATRIC ASSESSMENTS** section, the text defining complicated UTI should read 2 months (b) (4).

This corrected action letter incorporates the correction of the error. The effective action date will remain April 24, 2024, the date of the original letter.

This NDA provides for the use of Pivya (pivmecillinam) tablets for the treatment of female patients 18 years of age and older with uncomplicated urinary tract infections (uUTI) caused by susceptible isolates of *Escherichia coli*, *Proteus mirabilis*, and *Staphylococcus saprophyticus*.

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.

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

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

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 216483**." 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 Pivya (pivmecillinam) tablet shall be 36 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F); excursions permitted between 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 study requirement for ages birth to less than 2 months for uncomplicated urinary tract infections because necessary studies are impossible or highly impracticable. This is because the diagnosis of UTI in patients less than 2 months of age is, by definition, complicated UTI.

We are deferring submission of your pediatric studies for ages 2 months 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.

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

[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.

annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. These required studies are listed below:

4603-1 Conduct an open label single-dose safety, tolerability and pharmacokinetic study in pediatric subjects less than 12 years of age receiving systemic antibacterial therapy for the treatment of a suspected or confirmed bacterial infection.

Draft Protocol Submission:	08/2024
Final Protocol Submission:	12/2024
Study Completion:	02/2028
Final Report Submission:	08/2028

4603-2 Conduct a multicenter, randomized, single-blind study to evaluate the safety and tolerability of pivmecillinam hydrochloride versus nitrofurantoin for the treatment of pediatric subjects, 12 years to less than 18 years of age, with uncomplicated urinary tract infections.

Draft Protocol Submission:	07/2024
Final Protocol Submission:	11/2024
Study Completion:	05/2026
Final Report Submission:	11/2026

4603-3 Conduct a multicenter, randomized, single-blind study to evaluate the safety and tolerability of pivmecillinam hydrochloride versus an appropriate comparator for the treatment of pediatric subjects, 2 months to less than 12 years of age, with uncomplicated urinary tract infections.

Draft Protocol Submission:	12/2028
Final Protocol Submission:	03/2029
Study Completion:	07/2030
Final Report Submission:	01/2031

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]

Submit the protocol(s) to your IND 118650, 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**

[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.

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 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, and to identify unexpected serious risks of the presence of pivmecillinam in human breast milk resulting in adverse effects on the breastfed infant.

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 these serious risks.

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

4603-4 Conduct a lactation study (milk only) in lactating women who have received pivmecillinam to assess concentrations of pivmecillinam in breast milk using a validated assay and to assess the effects on the breastfed infant.

The timetable you submitted on April 18, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	07/2024
Final Protocol Submission:	11/2024
Study Completion:	11/2025
Final Report Submission:	05/2026

4603-5 Conduct a U.S. surveillance study over a five-year period after the introduction of pivmecillinam to the market to determine if resistance or decreased susceptibility to pivmecillinam is occurring in the target population of bacteria that are in the approved pivmecillinam label.

The timetable you submitted on April 18, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	09/2024
Final Protocol Submission:	12/2024
Study Completion:	06/2030
Interim Report Submission:	08/2026
	08/2027
	08/2028
	08/2029
Final Report Submission:	08/2030

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.[4]

Submit clinical protocol(s) to your IND 118650 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.

[4] 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.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4603-6 Conduct studies and generate data to finalize the regulatory dissolution specification (method and acceptance criterion) for the drug product (pivmecillinam tablets, 185 mg) to be used at batch release and for stability studies.

The timetable you submitted on March 22, 2024, states that you will conduct this study according to the following schedule:

Interim Report:	10/2024
Final Report:	05/2025

The final report should be submitted to your NDA as a prior approval supplement. The final report submission should be identified as "Final Report Submission for PMC 4603-6" in addition to being identified as a "Prior Approval Supplement".

Submit clinical protocols to your IND 118650 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**

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.*[5]

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] 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.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

REPORTING REQUIREMENTS

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

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 website[8].

If you have any questions, email Joseph Nguyen, PharmD, Regulatory Project Manager, at Joseph.Nguyen@fda.hhs.gov or call (301) 348-3937.

Sincerely,

{See appended electronic signature page}

Peter Kim, MD, MS
Director
Division of Anti-Infectives
Office of Infectious Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

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

[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[8] https://www.uspnf.com/

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/

PETER W KIM
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