



NDA 209445

NDA APPROVAL

Shionogi, Inc.
Attention: Ann Howell, PharmD, MS
Senior Director, Regulatory Affairs
300 Campus Drive
Florham Park, NJ 07932

Dear Dr. Howell:

Please refer to your New Drug Application (NDA) dated December 14, 2018, received December 14, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for FETROJA (cefiderocol) for injection, 1 gram per vial.

We acknowledge receipt of your major amendment dated April 12, 2019, which extended the goal date by three months.

This new drug application provides for the use of FETROJA (cefiderocol) for injection for the treatment of patients 18 years of age or older who have limited or no alternative treatment options for the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis caused by the following susceptible Gram-negative microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Enterobacter cloacae* complex.

Approval of this indication is based on limited clinical safety and efficacy data for FETROJA.

APPROVAL & LABELING

We have completed our review of this application, as amended, and 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 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 this 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 Specifications*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 209445.**” Approval of this submission by FDA is not required before the labeling is used.

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 deferring submission of your pediatric studies because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under 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:

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>.

3744-1 Conduct an open-label, randomized, multicenter, active-controlled trial to evaluate the pharmacokinetics, safety and tolerability of FETROJA (cefiderocol) in children from 3 months to less than 18 years of age with cUTI. The dose for this study for children 3 months to less than 12 years of age will be determined by the data from a single-dose, non-comparative study assessing the pharmacokinetics of FETROJA (cefiderocol) in pediatric patients from 3 months to less than 12 years of age with suspected or confirmed Gram-negative infections.

The timetable you submitted on November 12, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	Submitted
Final Protocol Submission:	Submitted
Study Completion:	12/2023
Final Report Submission:	04/2024

3744-2 Conduct an open-label, single arm non-comparative study to evaluate the pharmacokinetics, safety and tolerability of multiple doses of FETROJA (cefiderocol) in children from birth to less than 3 months of age with suspected or confirmed cUTI. The dose for this study will be determined by the data from a single-dose, non-comparative study assessing the pharmacokinetics of FETROJA (cefiderocol) in pediatric patients from birth to less than 3 months of age with suspected or confirmed Gram-negative infections.

The timetable you submitted on November 12, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	Submitted
Final Protocol Submission:	06/2022
Study Completion:	08/2024
Final Report Submission:	01/2025

Submit the protocol(s) to your IND 116787, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (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 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 the serious risk of increased mortality noted in patients with serious infections caused by carbapenem-resistant Gram-negative pathogens and the development of resistance to FETROJA (cefiderocol) in microorganisms specific to the cUTI indication in the label.

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:

3744-3 Conduct US surveillance studies for five years from the date of marketing FETROJA to determine if resistance to cefiderocol has developed in those organisms specific to the cUTI indication in the label.

The timetable you submitted on November 12, 2019, states that you will conduct these studies according to the following schedule:

Draft Protocol Submission: 01/2020
Final Protocol Submission: 06/2020
First Interim Report: 06/2021
Second Interim Report: 06/2022
Third Interim Report: 06/2023
Fourth Interim Report: 06/2024
Fifth Interim Report: 06/2025
Study Completion: 12/2025
Final Report Submission: 03/2026

3744-4 Conduct a study to define the mechanism(s) of resistance to FETROJA (cefiderocol) for isolates identified as being resistant to cefiderocol in the surveillance study (five years from the date of marketing).

The timetable you submitted on November 12, 2019, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 06/2020
Final Protocol Submission: 09/2020
Study Completion: 12/2025
Final Report Submission: 06/2026

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

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

3744-5 Submit the final study report for the completed CREDIBLE-CR trial (1424R2131), *“A Multicenter, Randomized, Open-label Clinical Study of S-649266 or Best Available Therapy for the Treatment of Severe Infections Caused by Carbapenem-resistant Gram-negative Pathogens”*.

The timetable you submitted on November 12, 2019, states that you will conduct this trial according to the following schedule:

Trial Completion: Completed
Final Report Submission: 03/2020

3744-6 Submit the final study report for the completed APEKS-NP trial, *“Clinical Study of S-649266 for the Treatment of Nosocomial Pneumonia Caused by Gram-negative Pathogens”*.

The timetable you submitted on November 12, 2019, states that you will conduct this trial according to the following schedule:

Trial Completion: Completed
Final Report Submission: 03/2020

Submit clinical protocol(s) to your IND 116787 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 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. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs*.³

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, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.⁴ Information and Instructions for completing the form can be found at FDA.gov.⁵ For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.⁶

³ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁴ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

⁶ <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>

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.⁷

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 J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

John Farley, MD, MPH
Acting Director
Office of Infectious Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

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

⁷ <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>

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
11/14/2019 05:03:00 PM