

# Press Release



## **FETROJA<sup>®</sup> (cefiderocol) Approved by the FDA for Treatment of Complicated Urinary Tract Infections (cUTI) in Adult Patients with Limited or No Alternative Treatment Options**

**FETROJA is the first approved antibiotic that functions as a siderophore  
FETROJA binds to free iron to gain additional cell entry  
FETROJA demonstrated higher response rates versus imipenem/cilastatin in a cUTI study**

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**OSAKA, Japan and FLORHAM PARK, N.J., November 14 and 15, 2019** – Shionogi & Co., Ltd. (hereafter “Shionogi”) today announced the U.S. Food and Drug Administration (FDA) has approved FETROJA<sup>®</sup> (cefiderocol) for patients 18 years of age or older who have limited or no alternative treatment options, for the treatment of complicated urinary tract infections (cUTI), 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.

“FETROJA will fill a very important unmet medical need because of its unique method of penetrating the cell wall of Gram-negative bacteria and its ability to overcome many of the resistance mechanisms that bacteria employ against antibiotics. Today’s approval represents Shionogi’s ongoing commitment to develop medicines that help fight these life-threatening infections in patients for whom limited or no alternative treatment options exist,” said Isao Teshirogi, Ph.D., president and CEO at Shionogi.

The approval of FETROJA is based on data from the pivotal APEKS-cUTI study, a multinational, multicenter, double-blind clinical trial that evaluated the efficacy and safety of FETROJA versus imipenem/cilastatin (IPM/CS) in patients with cUTI. Study results showed the response rates for the composite endpoint of microbiological eradication and clinical response at the test of cure (TOC) were significantly higher in the FETROJA arm compared to the IPM/CS arm. In the study, 72.6% (183/252) of patients in the FETROJA arm met the primary endpoint versus 54.6% (65/119) in the IPM/CS arm at TOC. The adjusted difference between the groups was 18.58% (95% CI: 8.2%, 28.2%). Clinical response rates at the TOC visit were similar between FETROJA and IPM/CS.

Serious adverse events were reported for 4.7% (14/300) of patients who received FETROJA and 8.1% (12/148) of patients who received IPM/CS. The most frequently occurring adverse reactions in greater than or equal to 2% of patients treated with FETROJA were diarrhea, infusion site reactions, constipation, rash, candidiasis, cough, elevations in liver tests, headache, hypokalemia, nausea, and vomiting. Please see Important Safety Information, Indications and Usage below.

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“In the pivotal study, cefiderocol achieved a higher response rate compared to imipenem/cilastatin,” said George H. Karam, M.D., MACP, Paula Garvey Manship Chair of Medicine at the Louisiana State University School of Medicine. “With today’s approval of cefiderocol, the infectious disease community now has a new type of antibiotic with a unique mechanism of cell entry to add to their toolkit to assist in the complexity of treating highly resistant pathogens that are occurring with increasing frequency in life-threatening infections.”

FETROJA was designated a Qualified Infectious Disease Product (QIDP) by the FDA, providing Fast Track designation and Priority Review. Shionogi anticipates making FETROJA commercially available in early 2020.

## About Gram-negative Infections

The increasing resistance of many infections caused by Gram-negative bacteria to existing therapies, including carbapenem-resistant Enterobacteriaceae and non-fermenting species such as *Pseudomonas aeruginosa* (*P. aeruginosa*), *Acinetobacter baumannii* (*A. baumannii*), and *Stenotrophomonas maltophilia* (*S. maltophilia*), poses a serious health challenge.<sup>1-5</sup> There is an increasing number of Gram-negative pathogens resistant to multiple antibiotics, making them difficult to treat and resulting in high mortality rates.<sup>6</sup> In the U.S., More than 2.8 million antibiotic-resistant infections occur in the United States each year, and more than 35,000 people die as a result.<sup>7</sup> In the EU, about 25,000 patients die from an infection with the selected multidrug-resistant bacteria.<sup>8</sup> The World Health Organization and the Centers for Disease Control and Prevention have identified carbapenem-resistant strains of Enterobacteriaceae, *P. aeruginosa*, and *A.baumannii* as the top priority in the research and development of new antibiotics.<sup>2,7</sup>

## About FETROJA® (cefiderocol) for injection

FETROJA® (cefiderocol) is a cephalosporin antibiotic with a novel mechanism for penetrating the outer cell membrane of Gram-negative pathogens by acting as a siderophore. In addition to entering cells by passive diffusion through porin channels, FETROJA binds to ferric iron and is actively transported into bacterial cells through the outer membrane via the bacterial iron transporters, which function to incorporate this essential nutrient for bacteria.<sup>9</sup> These mechanisms allow cefiderocol to achieve higher concentrations in the periplasmic space where it can bind to penicillin-binding proteins and inhibit cell wall synthesis in the bacterial cells.<sup>9</sup> FETROJA has also demonstrated *in vitro* activity against certain bacteria that contain very problematic resistant enzymes such as ESBLs, AmpC, serine- and metallo-carbapenemases.<sup>9</sup> Data from multinational surveillance studies for FETROJA demonstrated potent *in vitro* activity against a wide spectrum of Gram-negative pathogens including carbapenem-resistant *Acinetobacter baumannii* (*A. baumannii*), *Pseudomonas aeruginosa* (*P. aeruginosa*), Enterobacteriaceae, and *Stenotrophomonas maltophilia* (*S. maltophilia*).<sup>1</sup> The clinical

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significance of the *in vitro* data is unknown. FETROJA has poor *in vitro* activity against Gram-positive or anaerobic bacteria.

Shionogi also submitted a marketing authorization application for cefiderocol to the European Medicines Agency and it was accepted in March 2019.<sup>10</sup>

## Important Safety Information

### Contraindications

FETROJA® (cefiderocol) is contraindicated in patients with a known history of severe hypersensitivity to cefiderocol or other beta-lactam antibacterial drugs, or any other component of FETROJA.

### Warnings and Precautions

#### Increase in All-Cause Mortality in Patients with Carbapenem-Resistant Gram-Negative Bacterial Infections

An increase in all-cause mortality was observed in patients treated with FETROJA as compared to best available therapy (BAT) in a multinational, randomized, open-label trial in critically ill patients with carbapenem-resistant Gram-negative bacterial infections (NCT02714595). Patients with nosocomial pneumonia, bloodstream infections, sepsis, or cUTI were included in the trial. BAT regimens varied according to local practices and consisted of one-to-three antibacterial drugs with activity against Gram-negative bacteria. Most of the BAT regimens contained colistin.

The increase in all-cause mortality occurred in patients treated for nosocomial pneumonia, bloodstream infections, or sepsis. The 28-Day all-cause mortality was higher in patients treated with FETROJA than in patients treated with BAT [25/101 (24.8%) vs. 9/49 (18.4%), treatment difference 6.4%, 95% CI (-8.6, 19.2)]. All-cause mortality remained higher in patients treated with FETROJA than in patients treated with BAT through Day 49 [34/101 (33.7%) vs. 10/49 (20.4%), treatment difference 13.3%, 95% CI (-2.5, 26.9)]. Generally, deaths were in patients with infections caused by Gram-negative organisms, including nonfermenters such as *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, and *Pseudomonas aeruginosa*, and were the result of worsening or complications of infection, or underlying comorbidities. The cause of the increase in mortality has not been established. The safety and efficacy of FETROJA has not been established for the treatment of nosocomial pneumonia, bloodstream infections, or sepsis.

Reserve FETROJA for use in patients who have limited or no alternative treatment options for the treatment of cUTI. Closely monitor the clinical response to therapy in patients with cUTI.

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## **Hypersensitivity Reactions**

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported in patients receiving beta-lactam antibacterial drugs. Hypersensitivity was observed in FETROJA clinical trials. These reactions are more likely to occur in individuals with a history of beta-lactam hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe reactions when treated with cephalosporins. Before therapy with FETROJA is instituted, inquire about previous hypersensitivity reactions to cephalosporins, penicillins, or other beta-lactam antibacterial drugs. Discontinue FETROJA if an allergic reaction occurs.

## ***Clostridium difficile*-Associated Diarrhea (CDAD)**

*Clostridioides difficile*-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents, including FETROJA. CDAD may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *C. difficile*.

*C. difficile* produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary because CDAD has been reported to occur more than two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, antibacterial drugs not directed against *C. difficile* may need to be discontinued. Manage fluid and electrolyte levels as appropriate, supplement protein intake, monitor antibacterial treatment of *C. difficile*, and institute surgical evaluation as clinically indicated.

## **Seizures and Other Central Nervous System (CNS) Adverse Reactions**

Cephalosporins, including FETROJA, have been implicated in triggering seizures. Nonconvulsive status epilepticus (NCSE), encephalopathy, coma, asterixis, neuromuscular excitability, and myoclonia have been reported with cephalosporins particularly in patients with a history of epilepsy and/or when recommended dosages of cephalosporins were exceeded due to renal impairment. Adjust FETROJA dosing based on creatinine clearance. Anticonvulsant therapy should be continued in patients with known seizure disorders. If CNS adverse reactions including seizures occur, patients should undergo a neurological evaluation to determine whether FETROJA should be discontinued.

## **Development of Drug-Resistant Bacteria**

Prescribing FETROJA in the absence of a proven or strongly suspected bacterial infection or a

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prophylactic indication is unlikely to provide benefit to the patient and may increase the risk for development of drug-resistant bacteria.

## Adverse Reactions

The most common adverse reactions occurring in ( $\geq 2\%$ ) of patients receiving FETROJA compared to imipenem/cilastatin in clinical trials were: diarrhea (4% vs 6%), infusion site reactions (4% vs 5%), constipation (3% vs 4%), rash (3% vs  $<1\%$ ), candidiasis (2% vs 3%), cough (2% vs  $<1\%$ ), elevations in liver tests (2% vs  $<1\%$ ), headache (2% vs 5%), hypokalemia (2% vs 3%), nausea (2% vs 4%), and vomiting (2% vs 1%).

**Report side effects to the FDA at 1-800-FDA-1088 or <http://www.fda.gov/medwatch>. Report side effects to Shionogi Inc. at 1-800-849-9707.**

## Indications and Usage

### Indication

FETROJA<sup>®</sup> (cefiderocol) is indicated in patients 18 years of age or older who have limited or no alternative treatment options for the treatment of complicated urinary tract infections (cUTI), 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.

### Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of FETROJA and other antibacterial drugs, FETROJA should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

**For full Prescribing Information, please visit [Shionogi.com](http://Shionogi.com).**

## About Shionogi

Shionogi & Co., Ltd. is a Japanese major research-driven pharmaceutical company dedicated to bringing benefits to patients based on its corporate philosophy of “supplying the best possible medicine to protect the health and wellbeing of the patients we serve.” The company currently markets

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products in several therapeutic areas including anti-infectives, pain, cardiovascular diseases, and gastroenterology. Our pipeline is focused on infectious disease, pain, CNS, and oncology. For more information on Shionogi & Co., Ltd., visit [www.shionogi.co.jp/en](http://www.shionogi.co.jp/en). Shionogi Inc. is the U.S. subsidiary of Shionogi & Co., Ltd. based in N.J. For more information on Shionogi Inc., please visit <https://www.shionogi.com/>.

## Forward-Looking Statements

*This announcement contains forward-looking statements. These statements are based on expectations in light of the information currently available, assumptions that are subject to risks and uncertainties which could cause actual results to differ materially from these statements. Risks and uncertainties include general domestic and international economic conditions such as general industry and market conditions, and changes of interest rate and currency exchange rate. These risks and uncertainties particularly apply with respect to product-related forward-looking statements. Product risks and uncertainties include, but are not limited to, completion and discontinuation of clinical trials; obtaining regulatory approvals; claims and concerns about product safety and efficacy; technological advances; adverse outcome of important litigation; domestic and foreign healthcare reforms and changes of laws and regulations. Also, for existing products, there are manufacturing and marketing risks, which include, but are not limited to, inability to build production capacity to meet demand, unavailability of raw materials, and entry of competitive products. The company disclaims any intention or obligation to update or revise any forward-looking statements whether as a result of new information, future events, or otherwise.*

## For further information, contact:

Shionogi & Co., Ltd.

Corporate Communications

Telephone: +81-6-6209-7885

Fax: +81-6-6229-9596

Shionogi Inc. U.S. Media Contact

Lindsay Bohlander

Director, Advocacy & PR

+1 973-307-3718

[lindsay.bohlander@shionogi.com](mailto:lindsay.bohlander@shionogi.com)

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