PRESSRELEASE

SHIONOGI

Shionogi Presents Real-World Evidence Showing Strong Efficacy with Fetroja® (cefiderocol) Against Treatment Resistant Bacterial Infections at IDWeek 2022

- Real-world evidence demonstrated that Fetroja achieved clinical cure in 63% of patients with *Acinetobacter baumannii* infections (48/76) or *Pseudomonas aeruginosa* infections (76/120).

- In an analysis of early use experience, including compassionate use where patients had limited treatment options, 80% (74/92) of patients treated with Fetroja reported clinical cure for difficult-to-treat Gram-negative infections.

OSAKA, Japan, October 20, 2022 – Shionogi & Co., Ltd. (Head Office: Osaka, Japan; Chief Executive Officer: Isao Teshirogi, Ph.D.) announced that new Fetroja® (cefiderocol) data will be presented at IDWeek 2022 including new real-world evidence demonstrating Fetroja's strong efficacy against some of the most difficult-to-treat Gram-negative bacterial infections.

New data from PROVE (Retros**p**ective Cefide**ro**col Chart Re**vie**w) demonstrated that Fetroja achieved clinical cure in 63% (48/76) of patients with *Acinetobacter baumannii* infections and 63% (76/120) of patients with *Pseudomonas aeruginosa* infections. PROVE is an ongoing international retrospective study assessing real-world outcomes and safety of Fetroja in hospitalized patients with Gram-negative bacterial infections. Of the *Acinetobacter baumannii* infections, 96% were resistant to carbapenems (a last-line antibiotic), and 97% of the *Pseudomonas aeruginosa* infections were carbapenem-resistant.

Safety and tolerability data were generally consistent with the safety profile of Fetroja in clinical studies. Of the total cohort of 220 patients, five had adverse drug reactions (ADR), of which two had rashes, one had an increase in liver function test values, and two had diarrhea. One patient who was treated with Fetroja experienced a serious ADR (interstitial nephritis). Fetroja was withdrawn in two patients. For both *Acinetobacter baumannii* and *Pseudomonas aeruginosa* infections, 79% of patients were alive and 21% of patients died within 30 days of starting Fetroja (30-day all-cause mortality).

Additionally, in an analysis of early use experience, including compassionate use where patients had limited treatment options, 80% of patients treated with Fetroja reported clinical cure (74/92) for difficult-to-treat Gram-negative infections (including *Pseudomonas aeruginosa* and *Acinetobacter baumannii*). Adverse event (AE) data was reported for 53 patients, of whom 13 (24.5%) reported AEs and 40 (75.5%) did not.

"As the increasing threat of antimicrobial resistance continues to be recognized, it is important to show strong activity against resistant pathogens that the World Health Organization deems to be high-priority," said Simon Portsmouth, M.D., Shionogi's Vice President of Clinical Development. "Fetroja continues to demonstrate its important role in improving outcomes in patients infected with these highly resistant problematic pathogens."

The IDWeek 2022 abstracts and poster presentations are available to event registrants on the IDWeek 2022 website.

Antimicrobial resistance (AMR)
Antimicrobial resistance (AMR) is a major health burden that urgently needs to be addressed. In 2019, globally, approximately 1.27 million people died as a result of infections caused by resistant pathogens, surpassing deaths from HIV or malaria.[1]

Shionogi's commitment to fighting antimicrobial resistance
Shionogi has a strong heritage in the field of anti-infectives and has been developing antimicrobial therapies for more than 60 years. Shionogi is proud to be one of the few large pharmaceutical companies that continues to focus on research and development in anti-infectives. The company invests the highest proportion of its pharmaceutical revenues in relevant anti-infectives R&D compared to other large pharmaceutical companies. For more information, please refer to: https://www.shionogi.com/global/en/sustainability/amr.html.

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 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 https://www.shionogi.com/global/en/.

About Shionogi Inc.
Shionogi Inc. is the U.S. subsidiary of Shionogi & Co., Ltd., a 144-year-old global pharmaceutical company with headquarters in Osaka, Japan. In the U.S., Shionogi Inc. leverages our science-based heritage to develop and commercialize pharmaceutical products to treat unmet medical needs in infectious disease and other areas of high medical need including neurology and cardiovascular disease. For more information, please visit www.shionogi.com.

About cefiderocol
Cefiderocol for injection is the first and only siderophore cephalosporin antibiotic for the treatment of serious Gram-negative infections. It has 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, cefiderocol 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. These mechanisms allow cefiderocol to achieve high concentrations in the periplasmic space where it can bind to penicillin-binding proteins and inhibit cell wall synthesis in the bacterial cells. Cefiderocol has also demonstrated *in vitro* activity against certain bacteria that contain problematic resistant enzymes such ESBLs, AmpC, and serine- and metallo-carbapenemases. Data from multinational surveillance studies for cefiderocol demonstrated potent *in vitro* activity against a wide spectrum of Gram-negative pathogens including carbapenem-resistant *A. baumannii* complex, *P. aeruginosa*, Enterobacterales, and *S. maltophilia*. The clinical significance of the *in vitro* data is unknown. Cefiderocol has no clinically relevant *in vitro* activity against most Gram-positive bacteria and anaerobic bacteria.

U.S. INDICATIONS
Fetroja® (cefiderocol) is indicated in patients 18 years of age or older 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*.

Fetroja is indicated in patients 18 years of age or older for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, caused by the following susceptible Gram-negative microorganisms: *Acinetobacter baumannii complex, Escherichia coli, Enterobacter cloacae complex, Klebsiella pneumoniae, Pseudomonas aeruginosa*, and *Serratia marcescens*.

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.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Fetroja 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 1 to 3 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 non-fermenters such as *Acinetobacter baumannii* complex, *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.

Closely monitor the clinical response to therapy in patients with cUTI and HABP/VABP.

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-treated patients in 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.

***Clostridioides 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*.

Careful medical history is necessary because CDAD has been reported to occur more than 2 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 prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

ADVERSE REACTIONS
The most common adverse reactions occurring in (≥2%) of patients receiving Fetroja compared to imipenem/cilastatin in the cUTI trial 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%). The most common adverse reactions occurring in (≥4%) of patients receiving Fetroja compared to meropenem in the HABP/VABP trial were: elevations in liver tests (16% vs 16%), hypokalemia (11% vs 15%), diarrhea (9% vs 9%), hypomagnesemia (5% vs <1%), and atrial fibrillation (5% vs 3%).

Click here for Full U.S. Prescribing Information for Fetroja® (cefiderocol).

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, lack of availability 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.

Contact:
Danielle Lewis
+1 862-395-4034
Danielle.Lewis@shionogi.com

Reference:

1. Murray CJL, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis. *The Lancet*. 2022;399(10325):629-655. doi:10.1016/s0140-6736(21)02724-0