PRESSRELEASE

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IDWeek 2024: Shionogi Presents Largest Global Real-World Evidence Study of Cefiderocol Demonstrating Strong Clinical Response Rates Across Seriously Ill Patients

Additional presentations show potent in vitro activity for cefiderocol against emerging pathogens with limited treatment options, including those that are resistant to newer agents*

OSAKA, Japan, October 16, 2024 – Shionogi & Co., Ltd. (Head Office: Osaka, Japan; President & CEO: Isao Teshirogi, Ph.D.; hereafter "Shionogi") announces new data at IDWeek 2024 from PROVE (Retrospective Cefiderocol Chart Review), the largest global real-world evidence study of Fetroja®/Fetcroja® (cefiderocol), an innovative siderophore cephalosporin, for the treatment of seriously ill adult patients with certain Gram-negative (GN) bacterial infections, the majority of which were carbapenem-resistant (CR).

Please see below under About Cefiderocol the Full indications, and Important Safety Information of Fetroja in the U.S.

PROVE is an international, multicenter, retrospective medical chart review study designed to describe the patient characteristics and clinical outcomes in patients treated with cefiderocol for GN bacterial infections in real-world settings between 2020 and 2024.[1] Of the patients included in the analysis, 75.1% had a favorable clinical response to cefiderocol at the end of treatment (defined as resolution or improvement of signs and symptoms as judged by the physician, excluding deaths while on therapy).[1]

"Seriously ill patients with resistant Gram-negative bacterial infections are often difficult to treat. Although antibiotics are usually approved based on data from randomized controlled clinical trials, clinicians often rely on real-world evidence data to understand how antibiotics may perform in clinical settings," said Cornelius (Neil) Clancy, MD, Professor of Medicine, University of Pittsburgh. "This real-world evidence from PROVE, the largest to date for cefiderocol, further support its use and importance as a treatment option for appropriate patients with carbapenem-resistant Gram-negative infections in clinical settings."

This analysis included 1,075 hospitalized patients, the majority (56.6%) of whom were in the intensive care unit and had a median age of 60 (range from 46-69 years).[1] The majority (53.1%) of patients had respiratory tract infections (RTIs), 10.6% of patients had urinary tract infections (UTIs), and 10% of patients had bloodstream infections.[1] Additionally, 74.6% of infections were resistant to carbapenems, antibiotic agents commonly used for treatment of severe bacterial infections.[1,2] Of monomicrobial infections, the predominant pathogen was *Pseudomonas aeruginosa* (35.9%) followed by *Acinetobacter baumannii* (18.1%), and Enterobacterales (13.1%).[1] Also a quarter of patients (25.2%) had polymicrobial infections, where an infection involved multiple concurrent Gram-negative pathogens.[1]

Clinical response rates were 71.6% in patients with RTI, 74.1% in patients with bloodstream infections and 91.2% in patients with UTIs.[1] Overall, the rate of 30-day all-cause mortality (ACM) was 23.3%.[1] There were 29 adverse drug reactions (ADRs) across 25 patients, including three serious ADRs.[1] Of the 1,075 patients, 13 patients discontinued treatment with cefiderocol due to adverse drug reactions.[1]

Additional Studies Presented at IDWeek

High Rates of Cross-Resistance Were Observed Among Beta-lactam/Beta-lactamase Inhibitors, But Not with Cefiderocol
Data from two studies demonstrated the *in vitro** activity of cefiderocol against multidrug-resistant *Pseudomonas aeruginosa* and Enterobacterales isolates that were non-susceptible to several contemporary beta-lactam/beta-lactamase inhibitor (BL/BLI) combinations.[3,4] Cross-resistance, where bacteria are resistant to multiple distinct antibiotics within the same class, was observed at high rates between BL/BLI combinations, but not with cefiderocol.[3,4,5]

Cefiderocol Maintained Activity Against Highly Resistant Metallo-beta-lactamase Producing Bacteria
Also at IDWeek, data will be presented from two studies that demonstrated the *in vitro** activity of cefiderocol against bacteria that produce metallo-beta-lactamases (MBL), enzymes that can inactivate a majority of antibiotics.[6,7] MBL-producing bacteria are difficult-to-treat and are becoming increasingly prevalent around the world, with almost no treatment options.[8,9] These studies showed that cefiderocol was active against clinical isolates of *Pseudomonas aeruginosa* and Enterobacterales carrying MBL genes, including those that were nonsusceptible to carbapenems and BL/BLI combinations.[6,7]

"The findings of these studies provide insights on the dynamics where cross-resistance was observed among the beta-lactams and beta-lactamase inhibitor combinations where notably, cefiderocol demonstrated potent activity against isolates resistant to these inhibitor combinations. Additionally, cefiderocol showed activity against carbapenemase-producing Enterobacterales, especially isolates carrying metallo-beta-lactamases," said Jose Alexander, MD, Director of Microbiology, Virology and Immunology at AdventHealth. "This information can lead us to more rational antimicrobial susceptibility testing and enhance rapid therapy decisions based on resistance markers and specific carbapenemase detection."

**In vitro activity does not necessarily correlate with clinical efficacy.*

About Shionogi in Infectious Disease
Since 1953, Shionogi has been a leader in infectious disease discovery and commercialization. Our R&D story extends beyond antibiotics to include novel medications for HIV and influenza. Today, our global pipeline includes investigational agents developed to address global health challenges including antimicrobial resistance, COVID-19, influenza, rare fungal diseases and respiratory syncytial virus.

As part of our commitment to addressing unmet medical needs, Shionogi is partnering with several non-governmental organizations to increase equitable access to our medications worldwide. Shionogi has a landmark license and technology transfer agreement for cefiderocol with Global Antibiotic Research and Development Partnership (GARDP) and a collaboration agreement with the Clinton Health Access Initiative (CHAI) to transform the landscape of access to antibiotics in many low-income countries, most lower-middle and upper middle-income countries, and select high-income countries.

About Shionogi & Co. Ltd.
Shionogi & Co., Ltd. is a leading global 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 well-being of the patients we serve." Shionogi has discovered and developed novel antibiotics and medicines for HIV and influenza and currently markets medicines for infectious diseases and central nervous system disorders. Shionogi's global pipeline includes research programs in infectious diseases, pain/CNS,

metabolic disorders, rare diseases, oncology and stroke. For more information, visit https://www.shionogi.com/global/en/.

Antimicrobial Resistance

AMR is a major health burden that urgently needs to be addressed.[10] Globally, in 2019, there were 1.27 million deaths attributable to bacterial AMR.[10] Infections caused by carbapenem-resistant Gram-negative bacteria are often associated with a high mortality rate.[11] If no action is taken, drug-resistant pathogens could cause more than 39 million deaths over the next 25 years.[12]

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. For more information, please refer to: https://www.shionogi.com/global/en/sustainability/amr.html.

About Cefiderocol

In Europe, cefiderocol is commercially available under the brand name Fetcroja® for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options.[13] In the U.S., cefiderocol is available under the brand name Fetroja® and is indicated in patients 18 years of age or older for the treatment of hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia (HABP/VABP) and complicated urinary tract infections (cUTIs) caused by certain susceptible Gram-negative microorganisms.[14] In Japan, cefiderocol is commercially available under the brand name Fetroja® and received manufacturing and marketing approval from the Ministry of Health, Labour and Welfare for various infections caused by strains resistant to carbapenem antibiotics among sensitive strains of *Escherichia coli, Citrobacter species, Klebsiella pneumoniae, Enterobacter species, Serratia marcescens, Proteus species, Morganella morganii, Pseudomonas aeruginosa, Burkholderia species, Stenotrophomonas maltophilia,* and *Acinetobacter species.*

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 (HABP/VABP), 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 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 28-day all-cause mortality was observed in Fetroja-treated nosocomial pneumonia, bloodstream infections, or sepsis patients compared to those treated with best available therapy (BAT) in a clinical study (NCT02714595). Most BAT regimens contained colistin. All-cause mortality remained higher in patients treated with Fetroja than in patients treated with BAT through Day 49.

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 with Fetroja. Before Fetroja is instituted, inquire about previous hypersensitivity to cephalosporins, penicillins, or other beta-lactam drugs. If an allergic reaction occurs, discontinue Fetroja.

Clostridioides difficile-associated Diarrhea (CDAD)

CDAD has been reported with nearly all systemic antibacterial agents, including Fetroja. 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.

Seizures and Other Central Nervous System (CNS) Adverse Reactions

Cephalosporins, including Fetroja, have been implicated in triggering CNS adverse reactions such as seizures. Encephalopathy, coma, asterixis, and neuromuscular excitability 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. If focal tremors or seizures occur, evaluate patients 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 in the cUTI trial were: diarrhea (4%), infusion site reactions (4%), constipation (3%), rash (3%), candidiasis (2%), cough (2%), elevations in liver tests (2%), headache (2%), hypokalemia (2%), nausea (2%), and vomiting (2%). The most common adverse reactions occurring in ≥4% of patients receiving Fetroja in the HABP/VABP trial were: elevations in liver tests (16%), hypokalemia (11%), diarrhea (9%), hypomagnesemia (5%), and atrial fibrillation (5%).

Please 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.

For Further Information, Contact:

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