NEWS RELEASE

IDWeek 2023: Shionogi Presents New Real-World Evidence Demonstrating Effectiveness of Earlier Treatment with Fetroja® (cefiderocol) in Appropriate Patients

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Analysis from a retrospective multicenter observational study showed earlier treatment resulted in a reduction of in-hospital all-cause mortality in patients with Gram-negative infections who previously received other antibiotics, including those with difficult-to-treat pathogens

OSAKA, Japan--(BUSINESS WIRE)-- Shionogi & Co., Ltd. (Head Office: Osaka, Japan; Chief Executive Officer: Isao Teshirogi, Ph.D.; hereafter "Shionogi") announced that it will present real-world evidence (RWE) suggesting treatment with Fetroja® (cefiderocol) is effective in treating Gram-negative infections and that appropriate patients who received Fetroja earlier (within 6-20 days of index culture) had lower in-hospital all-cause mortality (IHACM) than those receiving it later (>20 days).1 The data are being presented at IDWeek 2023, which is taking place in Boston, October 11-15.

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.2

“This retrospective real-world study of Fetroja in hospitalized patients highlights the complicated patient characteristics where difficult-to-treat Gram-negative infections require rapid treatment with an appropriate antibiotic. This analysis suggested earlier treatment with Fetroja in high-risk patients resulted in better outcomes

and lower mortality, though further investigations are needed to confirm the mortality finding," said Simon Portsmouth, MBChB, MD, FRCP, Senior Vice President, Head of Clinical Development, Shionogi. "Seriously ill patients are often not represented in randomized clinical trials due to the difficulty with interpreting outcomes in such confounding situations. With real-world evidence, we can identify opportunities to understand and optimize patient outcomes."

Seriously Ill Patient Population

The analysis, based on a retrospective multicenter observational study from the Premier Healthcare Database, included outcomes for 275 adult patients who were hospitalized between January 2020 and June 2022 and treated with Fetroja consecutively for ≥3 days after laboratory-confirmed Gram-negative infections. The patients included in this analysis did not have COVID-19.

The patients included in this analysis were generally seriously ill and half (53.1%) were in the intensive care unit. More than half (56.7%) had difficult-to-treat pathogens that were resistant to other antibiotics. Infection sites included respiratory (45.8%), urinary (19.6%), wound (18.2%) and blood (16.4%). In addition to Gram-negative infections, patients also had serious comorbidities including renal disease (42.9%), chronic pulmonary disease (36.7%), diabetes (34.9%) and congestive heart failure (32.7%).

The most common pathogens identified among patients were Pseudomonas aeruginosa (48.7%), Acinetobacter baumannii (23.6%), Klebsiella pneumoniae (14.2%),and Stenotrophomonas maltophilia(13.1%). More than one third of patients (34%) were infected with two or more pathogens. Fetroja was used as monotherapy in 33% of patients (n=92), though most patients (92%, n=253) had received other antibiotics prior to Fetroja.

In clinical trials, Fetroja demonstrated clinical efficacy against Acinetobacter baumannii, Pseudomonas aeruginosa and Klebsiella pneumoniae and showed in vitro activity against Stenotrophomonas maltophilia.In vitro activity does not necessarily correlate with clinical efficacy.

Earlier Treatment Initiation: Observed Effect on Outcomes

This analysis found overall in-hospital all-cause mortality (IHACM) among patients receiving Fetroja was 16.4% (95%CI:12.0%-20.7%). Among patients for whom treatment with Fetroja was initiated within 5 days of index culture (n=135), the IHACM was 10.4% [5.2%–15.5%]. When treatment was initiated within 6-20 days of index culture (n=108), the IHACM was 19.4% [12%–26.9%] and when treatment was initiated at more than 20 days (n=32), IHACM was 31.3% [8.2%–15.2%].

"This real-world evidence demonstrates the clinical utility of Fetroja in the treatment of adult patients with culture-

confirmed Gram-negative infections," said Thomas Lodise, PharmD, PhD, Associate Professor, Albany College of Pharmacy and Health Sciences. "The timing of treatment in relation to index culture findings suggest there are situations where it is appropriate to shift from antibiotic escalation strategies toward early, targeted administration of Fetroja as a measure to improve patient outcomes."

RWE studies can complement clinical evidence derived from randomized-controlled trials (RCT) and provide real-world data on the safety and effectiveness of a medical product.3,4,5 While RCT provide evidence of efficacy, real-world studies help improve understanding of effectiveness, safety, and economic performance in clinical settings.3,4,5 Real-world data on antimicrobials may better reflect the clinical setting in which therapeutic interventions are applied and can help contextualize the limitations of clinical trials.3,4

The IDWeek 2023 abstracts and poster presentations are available to congress registrants on the **IDWeek 2023 website**.

Antimicrobial Resistance

Antimicrobial resistance (AMR) is a major health burden which urgently needs to be addressed. Globally, in 2019, there were 1.27 million deaths attributable to bacterial AMR.6 Infections caused by carbapenem-resistant Gram-negative bacteria are often associated with a high mortality rate.7 If no action is taken, antimicrobial resistance is predicted to kill 10 million people every year by 2050, at a cumulative cost to global economic output of 100 trillion USD.8

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 Shionogi

Shionogi & Co., Ltd. is a leading global research-driven pharmaceutical company based in Japan 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." The company has discovered and developed novel medicines for HIV, influenza and antimicrobial resistance and currently markets products in several therapeutic areas including anti-infectives with the first siderophore cephalosporin. We are working to solve healthcare social issues by identifying disease areas with great social needs as core areas for research and development, with a focus on

infectious diseases. For more information on Shionogi & Co., Ltd., visit **https://www.shionogi.com/global/en/**

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 (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%).

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.

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