PRESSRELEASE

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ECCMID 2023: Shionogi Announces Real-World Evidence Demonstrating the Efficacy of Fetcroja® / Fetroja® (cefiderocol) Against Some of the Most Difficult-to-Treat Gram-Negative Bacterial Pathogens

A retrospective chart review interim analysis demonstrated that cefiderocol achieved clinical cure in 65% and 60% of patients with *Pseudomonas aeruginosa* and *Acinetobacter baumannii* respectively, the majority of whom were severely ill with comorbidities.

OSAKA, Japan, APRIL 17, 2023 - Shionogi & Co., Ltd. (Head Office: Osaka, Japan; Chief Executive Officer: Isao Teshirogi, Ph.D.; hereafter "Shionogi") announces key data for Fetcroja® (cefiderocol), an innovative siderophore cephalosporin, to be presented at the 33rd European Congress of Clinical Microbiology & Infectious Diseases (ECCMID), April 15-18, 2023, including new real-world evidence demonstrating its efficacy against some of the most difficult-to-treat Gram-negative bacterial infections.

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.[1] In the US, 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]

Interim results are emerging from PROVE (Retrospective Cefiderocol Chart Review), an ongoing international, retrospective study of the real-world use of cefiderocol for Gram-negative infections across EU and US sites.[3,4] The study includes 194 patients with *Pseudomonas aeruginosa* infections treated with cefiderocol (123 from the US and 71 from the EU). These were generally seriously ill patients, many requiring mechanical ventilation and/or vasopressor support. The interim results show that cefiderocol achieved clinical cure in 65% of these patients, and 81% of patients were alive within 30 days of starting cefiderocol treatment. The patients principally had respiratory tract and bloodstream infections. Cefiderocol was initiated for a documented pathogen in the majority of cases (77%), and as monotherapy in 57% of patients.

Also in the study were 98 patients with *Acinetobacter baumannii* infections (71 from US and 27 from the EU). The patients had respiratory infection and bacteraemia as the most common infections. High levels of organ support were required in these patients, with 45% receiving mechanical ventilation and 30% requiring vasopressor support. Cefiderocol achieved clinical cure in 60% of patients, and 76% of patients were alive within 30-days of starting treatment. Cefiderocol was targeted as first treatment or as salvage therapy in 93% of patients, and as monotherapy in 41% of patients.

"These interim results from PROVE build on a growing body of real-world evidence across Europe and the US demonstrating the efficacy of cefiderocol in treating patients with life-threatening infections, such as Acinetobacter baumannii and Pseudomonas aeruginosa, the majority of whom are very sick with multiple comorbidities," commented Prof. Dr. Dominic Wichmann, Consultant in department of Intensive Care Medicine, University of Hamburg-Eppendorf. *"These are pathogens that fall into the World Health*

Organization's critical priority list, for which effective treatments are urgently needed."

Antimicrobial resistance (AMR)
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.[5] Infections caused by carbapenem-resistant Gram-negative bacteria are often associated with a high mortality rate.[6] 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.[7]

About FETCROJA® (Cefiderocol)
Cefiderocol is a siderophore cephalosporin antibiotic with an innovative 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.[8] 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.[9] Cefiderocol has also demonstrated *in vitro* activity against certain bacteria that contain very problematic resistant enzymes such as ESBLs, AmpC, serine- and metallo-carbapenemases.[10,11] 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, P. aeruginosa*, Enterobacterales, and *S. maltophilia*.[12] The clinical significance of the *in vitro* data is unknown. Cefiderocol has no clinically relevant activity against Gram-positive or anaerobic bacteria.

FETCROJA® (Cefiderocol) INDICATION
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.

FETROJA® (Cefiderocol) US 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).

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.[13]

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

About Shionogi
Shionogi & Co., Ltd. is a 145-year-old global, research-driven pharmaceutical company headquartered in Osaka, Japan, that is 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, CNS disorders, cardiovascular diseases and gastroenterology. Shionogi's research and development currently target two therapeutic areas: infectious diseases, and pain/CNS disorders.

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

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:
SHIONOGI Website Inquiry Form : https://www.shionogi.com/global/en/contact.html

References

[1] FETCROJA SMPC. Available at: https://www.ema.europa.eu/en/documents/product-information/fetcroja-epar-product-information_en.pdf Last accessed March 2023

[2] Fetroja FDA prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209445s002lbl.pdf Last accessed March 2023

[3] Larcher R, *et al.* Real-world use of cefiderocol in the EU and US for Pseudomonas aeruginosa: interim data from the PROVE study. ECCMID abstract P2274

[4] Timsit JF, *et al.* Real-world use of cefiderocol in the EU and US for *Acinetobacter baumannii*: interim data from the PROVE study. ECCMID abstract P2272

[5] Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet 2022; 399: 629–55

[6] Perez F, et al. 'Carbapenem-Resistant Enterobacteriaceae: A Menace to our Most Vulnerable Patients'. Cleve Clin J Med. Apr 2013; 80(4): 225–33

[7] O'Neill. The Review on antimicrobial resistance. 2016. Available at: https://amr review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf Last accessed March 2023

[8] Ito A, Nishikawa T., Masumoto S, et al. Siderophore Cephalosporin Cefiderocol Utilizes Ferric Iron Transporter Systems for Antibacterial Activity against Pseudomonas aeruginosa. *Antimicrob Agents Chemother*. 2016;60(12):7396-7401

[9] Tillotson GS. Trojan Horse Antibiotics—A Novel Way to Circumvent Gram-Negative Bacterial Resistance? *Infectious Diseases: Research and Treatment*. 2016;9:45-52 doi:10.4137/IDRT.S3156

[10] K Kazmierczak *et al.* In vitro activity of cefiderocol, a siderophore cephalosporin, against a recent collection of clinically relevant carbapenem-non-susceptible Gram-negative bacilli, including serine carbapenemase- and metallo-β-lactamase-producing isolates (SIDERO-WT-2014 Study).). *International Journal of Antimicrobial Agents*, 2019; 53(2) 177-184

[11] A Ito *et al.* In Vitro Antibacterial Properties of Cefiderocol, a Novel Siderophore Cephalosporin, against Gram-Negative Bacteria. *Antimicrobial Agents and Chemotherapy,* 2018, 62:e01454-17.

[12] M Hackel, M Tsuji, Y Yamano, et al. In Vitro Activity of the Siderophore Cephalosporin, Cefiderocol, Against a Recent Collection of Clinically Relevant Gram-Negative Bacilli from North America and Europe, Including Carbapenem Non-Susceptible Isolates: The SIDERO-WT-2014 Study. *Antimicrobial Agents Chemotherapy*. 2017;61(9)

[13] Antimicrobial Resistance Benchmark 2021. https://accesstomedicinefoundation.org/medialibrary/resources/61ee760d03810_Antimicrobial%20Resistance%20Benchmark%20report%202021.pdf Last accessed March 2023