SHIONOGI ANNOUNCES FDA APPROVAL OF FETROJA® (CEFIDEROCOL) FOR THE TREATMENT OF HOSPITAL-ACQUIRED BACTERIAL PNEUMONIA AND VENTILATOR-ASSOCIATED BACTERIAL PNEUMONIA

OSAKA, Japan and FLORHAM PARK, N.J., September 28 and 29, 2020 – Shionogi & Co., Ltd. (hereafter "Shionogi") today announces that the U.S. Food and Drug Administration (FDA) has approved a supplemental New Drug Application (sNDA) for FETROJA® (cefiderocol) for the treatment of patients 18 years of age or older with 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*.

"Antimicrobial resistance is a major global health concern, and there is a clear need for new treatments such as FETROJA to give clinicians more options to fight life-threatening infections caused by Gram-negative pathogens," said Akira Kato, Ph.D., president and CEO at Shionogi Inc. "This milestone represents Shionogi's long-standing and unwavering commitment to constantly fight evolving infectious diseases in an era realizing significant unmet needs."

This expanded indication is based on the results of the Phase III APEKS-NP study, which showed FETROJA met the primary endpoint of non-inferiority compared to high-dose extended-infusion meropenem in all-cause mortality 14 days after initiation of study drug in the treatment of patients with HABP, VABP and healthcare-associated bacterial pneumonia (HCABP).

"Nosocomial pneumonia is one of the most common hospital-acquired infections and a rising number are caused by difficult-to-treat, multidrug-resistant pathogens, which can be a deadly threat for patients," said APEKS-NP principal investigator Richard G. Wunderink, M.D., Northwestern University Feinberg School of Medicine. "The results from the APEKS-NP study show that cefiderocol is a much-needed additional option for the treatment of patients with HABP and VABP due to multidrug-resistant Gram-negative bacteria."

FETROJA is currently approved for patients 18 years of age or older for the treatment of complicated urinary tract infections, including pyelonephritis, caused by Gram-negative pathogens. It is the first approved antibiotic that functions as a siderophore and has a novel mechanism for penetrating the outer cell membrane of Gram-negative pathogens including carbapenem-resistant strains. See the full indication below.

About APEKS-NP

APEKS-NP (***A****cinetobacter baumannii*, ***P****seudomonas aeruginosa*, ***E****scherichia coli*, ***K****lebsiella pneumoniae* and ***S****tenotrophomonas maltophilia* in **N**osocomial **P**neumonia) was a multinational, multicenter, double-blind, randomized, trial designed to evaluate the efficacy and safety of FETROJA for the treatment of nosocomial pneumonia including HABP, VABP, and HCABP caused by Gram-negative pathogens. Patients were randomized on a 1:1 basis to receive FETROJA administered by intravenous infusion of two grams over a three-hour period every eight hours or high-dose extended-infusion meropenem administered as two grams over a three-hour period every eight hours, for seven to 14 days in the hospital. Linezolid was additionally administered for at least five days in both arms to provide coverage for methicillin-resistant *Staphylococcus aureus* (MRSA), and for Gram-positive bacteria in the FETROJA group. Safety was investigated up to 28 days after the end of treatment unless there was an ongoing adverse event(s) which were followed up until their resolution.

The study found that FETROJA:

- Met the primary endpoint of non-inferiority to high-dose meropenem, infused over three hours. At Day 14, all-cause mortality (ACM) in the modified intent-to-treat population was 12.4% for FETROJA (18/145) and 12.2% for high-dose meropenem (18/147), respectively (difference: 0.2, 95% CI: –7.2; 7.7)
- Met key secondary endpoints of clinical outcomes at test of cure (TOC) defined as seven days after treatment, and Day 28 ACM:
    - Clinical outcome at TOC: 64.8% (94/145) FETROJA versus 66.7% (98/147) meropenem high dose (difference: –2.0, 95% CI: –12.5; 8.5)
    - Day 28 ACM: 22.1% (32/145) FETROJA versus 21.1% (31/147) meropenem high dose (difference: 1.1, 95% CI: –8.2; 10.4)

- Demonstrated no unexpected safety signals the incidence of treatment-emergent adverse events was similar between treatment arms:
    - 87.8% (130/148) for FETROJA versus 86% (129/150) for meropenem high dose (difference: 1.8; 95% CI: –5.8 to 9.5)

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. These mechanisms allow FETROJA 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. FETROJA has also demonstrated in vitro activity against certain bacteria that contain very problematic resistant enzymes such as ESBLs, AmpC, serine- and metallo-carbapenemases. Data from multinational surveillance studies for FETROJA demonstrated potent in vitro activity against a wide spectrum of Gram-negative pathogens including carbapenem-resistant *A. baumannii*, *P. aeruginosa*, Enterobacterales, and *S. maltophilia*. The clinical significance of the *in vitro* data is unknown. FETROJA has poor *in vitro* activity against Gram-positive or anaerobic bacteria.

Cefiderocol, under the brand name FETCROJA®, is approved by the European Commission for the treatment of infections due to aerobic Gram-negative bacteria in adults 18 years or older with limited treatment options.

Indications and Usage

Indication from USPI

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%).

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.

For full Prescribing Information, please visit Shionogi.com.

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.[1]
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/. Shionogi Inc. is the U.S. subsidiary of Shionogi & Co., Ltd. based in N.J. For more information on Shionogi Inc., please visit www.shionogi.com.

Forward Looking Statement

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.

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