Press Release

FDA Accepts Shionogi's Supplemental New Drug Application with Priority Review for FETROJA® (cefiderocol) for the Treatment of Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia

OSAKA, Japan and FLORHAM PARK, N.J., June 1 and 2, 2020 – Shionogi & Co., Ltd. (hereafter "Shionogi") today announced the U.S. Food and Drug Administration (FDA) has accepted the company's supplemental New Drug Application (sNDA) for FETROJA® (cefiderocol) and granted Priority Review designation with a Prescription Drug User Fee Act (PDUFA) date of September 27, 2020. Shionogi submitted the sNDA for FETROJA for the treatment of adult patients with hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) caused by susceptible Gram-negative pathogens. HABP and VABP are also sometimes referred to as nosocomial pneumonia (NP).

"We are committed to working with the FDA in order to bring FETROJA to more patients fighting these challenging and life-threatening Gram-negative infections as quickly as possible," said Akira Kato, Ph.D., president and CEO at Shionogi Inc. "This submission represents our heritage in and commitment to developing antimicrobial therapies and filling unmet needs in the field of infectious disease."

The sNDA is based on results from 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).

The FDA approved FETROJA in November 2019 for patients 18 years of age or older who have limited or no alternative treatment options, 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, non-inferiority 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 (two grams) extended-infusion (over three-hours) meropenem administered 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 serious adverse event(s).

The study, which was first presented in October 2019 at IDWeek, 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 11.6% for high-dose meropenem (17/146), respectively (difference: 0.8, 95% CI: –6.6; 8.2)
- Met key secondary endpoints of clinical and microbiological 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)
    - Microbiological eradication at TOC: 47.6% (59/124) FETROJA versus 48% (61/127) meropenem high dose (difference: –1.4, 95% CI: –13.5; 10.7)
    - Day 28 ACM: 21.0% (30/143) FETROJA versus 20.5% (30/146) meropenem high dose (difference: 0.5, 95% CI: –8.7; 9.8)
- 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*, Enterobacteriaceae, 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.

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 50 years. Shionogi is proud to be one of the few large pharmaceutical companies that continue 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] See more about Shionogi's dedication to antimicrobial resistance (AMR) 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 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, 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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References

1. Access to Medicine Foundation. Antimicrobial Resistance Benchmark 2020. Retrieved from https://accesstomedicinefoundation.org/media/uploads/downloads/5e270aa36821a_Antimicrobial_Resistance_Benchmark_2020.pdf.