Press Release

U.S. FDA Advisory Committee Recommends Approval of Cefiderocol for Treatment of Complicated Urinary Tract Infections

OSAKA, Japan and FLORHAM PARK, N.J., October 16 and 17, 2019 – Shionogi & Co., Ltd. (hereafter "Shionogi") today announced that the U.S. Food and Drug Administration's (FDA) Antimicrobial Drugs Advisory Committee voted to recommend approval of the investigational antibiotic cefiderocol for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis, in patients with limited or no alternative treatment options. The Advisory Committee voted 14 to 2 that Shionogi provided substantial evidence about the efficacy and sufficient evidence of the safety of cefiderocol as part of its New Drug Application (NDA).

"We are pleased with the positive recommendation for the approval of cefiderocol for the treatment of cUTI. We appreciate the conscientious review of our data by the committee members and will continue to work closely with the FDA as it completes the review of our submission," said Isao Teshirogi, Ph.D., president and CEO. "Patients with cUTIs caused by Gram-negative pathogens continue to face a serious challenge with high morbidity and mortality rates. If approved, we believe cefiderocol could help address a significant unmet need in an area with limited treatment options to fight these life-threatening infections."

The Advisory Committee provides the FDA with independent advice and recommendations. The FDA is not bound by the committee's guidance, but takes its recommendation into consideration when reviewing investigational medicines. Cefiderocol was designated as a Qualified Infectious Disease Product (QIDP) by the FDA. Under this designation, cefiderocol was granted Fast Track status for its potential as a new antibiotic to treat serious or life-threatening conditions and to address unmet medical needs. The assigned action date is November 14, 2019 under the Prescription Drug User-Fee Act (PDUFA).

If approved, cefiderocol will be marketed under the brand name FETROJA®.

For additional information about the October 16, 2019 Advisory Committee meeting, please visit https://www.fda.gov/advisory-committees/advisory-committee-calendar/october-16-2019-antimicrobial-drugs-advisory-committee-meeting-announcement-10162019-10162019.

About Cefiderocol–An Investigational Antibiotic Agent

Cefiderocol is a siderophore cephalosporin with a novel mechanism for penetrating the outer cell membrane of Gram-negative pathogens including multidrug-resistant strains. It has a unique ability to overcome all three major mechanisms of carbapenem resistance (porin channel alterations, beta-lactamase inactivation, and efflux pump overproduction). 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.[1] In addition, cefiderocol can also enter cells by passive diffusion through porin channels and is stable against all known classes of beta-lactamases, including both the metallo- and serine-beta-lactamases.[2] 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.[3] Data from multinational surveillance studies for cefiderocol demonstrated potent *in vitro* activity against a wide spectrum of Gram-negative pathogens including carbapenem-resistant *Acinetobacter baumannii (A. baumannii), Pseudomonas aeruginosa (P. aeruginosa),* Enterobacteriaceae, and *Stenotrophomonas maltophilia (S. maltophilia).*[4] Cefiderocol has poor *in vitro* activity against Gram-positive or anaerobic bacteria. The clinical significance of *in vitro* data is unknown.

Shionogi submitted a New Drug Application to the U.S. Food and Drug Administration (FDA). Cefiderocol was designated as a Qualified Infectious Disease Product (QIDP) by the FDA with the assigned action date of November 14, 2019 under the Prescription Drug User-Fee Act (PDUFA). Additionally, Shionogi also submitted a marketing authorization application of cefiderocol to the European Medicines Agency and it was accepted in March 2019.[5]

About Gram-negative Infections

The increasing resistance of many infections caused by Gram-negative bacteria to existing therapies, including carbapenem-resistant Enterobacteriaceae and non-fermenting species such as *P. aeruginosa*, *A. baumannii*, and *S. maltophilia*, means there is a critical need for new, effective therapies.[4, 6-9] There are an increasing number of Gram-negative pathogens resistant to multiple antibiotics, making them difficult to treat and resulting in high mortality rates.[10] In the U.S., at least two million people are infected with antibiotic-resistant bacteria, and at least 23,000 people die as a result each year.[11] In the EU, about 25,000 patients die from an infection with the selected multidrug-resistant bacteria.[12] The World Health Organization and the Centers for Disease Control and Prevention have identified carbapenem-resistant strains of Enterobacteriaceae, *P. aeruginosa,* and *A.baumannii* as the top priority in the research and development of new antibiotics.[6,11]

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 www.shionogi.co.jp/en. Shionogi Inc. is the U.S. subsidiary

of Shionogi & Co., Ltd. based in N.J. For more information on Shionogi Inc., please visit https://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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