FOR EUROPEAN MEDICAL AND PHARMA TRADE MEDIA ONLY

SHIONOGI RECEIVES EUROPEAN COMMISSION MARKETING AUTHORISATION FOR FETCROJA® (CEFIDEROCOL) FOR THE TREATMENT OF INFECTIONS DUE TO AEROBIC GRAM-NEGATIVE BACTERIA IN ADULTS WITH LIMITED TREATMENT OPTIONS

- FETCROJA® (cefiderocol) has received European Commission (EC) marketing authorisation for the treatment of infections due to aerobic Gram-negative bacteria in adults with limited treatment options[1]
- The approval was based on non-clinical data and the PK/PD package (including *in vitro* data) and supported by the clinical data from three key studies submitted by Shionogi
- Cefiderocol is the first treatment which provides coverage against all Gram-negative pathogens considered of critical priority by the WHO – carbapenem-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and Enterobacteriaceae[2,3]
- Cefiderocol is the world's first siderophore cephalosporin that uses the bacteria's own iron uptake system to gain entry into the cell, acting like a Trojan horse[4]
- Antimicrobial resistance (AMR) is a major health burden which results in ~25,000 patients' deaths per year in the EU from an infection with multidrug-resistant bacteria[5], so new and effective treatment options are urgently needed

OSAKA, Japan and AMSTERDAM, NL, 28 April 2020 – Shionogi & Co., Ltd. (Head Office: Osaka, Japan; President & CEO: Isao Teshirogi, Ph.D.) and its European subsidiary, Shionogi B.V. (hereafter "Shionogi") today announces that the European Commission (EC) has granted a marketing authorisation for cefiderocol, a new antibiotic for the treatment of infections due to aerobic Gram-negative bacteria in adults (18 years or older) with limited treatment options.[1]

Cefiderocol has extensive *in vitro* activity against a broad spectrum of aerobic Gram-negative pathogens.

The EC approval of cefiderocol was based on the non-clinical data package, including the PK/PD data package. Data from multinational surveillance studies for cefiderocol demonstrated potent *in vitro* activity against a broad spectrum of aerobic Gram-negative pathogens including all three WHO critical priority

pathogens: carbapenem-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and Enterobacterales[2,3], as well as *Stenotrophomonas maltophilia*. [6] Cefiderocol also demonstrated *in vitro* activity against certain bacteria that contain very problematic resistant enzymes such as ESBLs, AmpC, serine- and metallo-carbapenemases.[7,8]

Cefiderocol clinical trials

Data from three clinical studies: APEKS-cUTI and APEKS-NP and CREDIBLE-CR supported the marketing authorisation of cefiderocol.[1] Data from the studies demonstrated the efficacy of cefiderocol in patients with the following types of infection: complicated urinary tract infections (cUTI) [9]; hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), sepsis (including complicated intra-abdominal infection (cIAI) and skin and skin structure infection (SSSI)) and patients with bacteraemia (some with no identified primary focus of infection). One of the studies included patients with Gram-negative infections caused by multidrug-resistant pathogens including carbapenem-resistant bacteria from the WHO priority list. [1]

"Antimicrobial resistance is a growing global health threat that is only set to get worse if no action is taken, so it is very welcome news that this new and effective antibiotic has now been approved in Europe," said Prof. Peter Hawkey, Institute of Microbiology and Infection College of Medical and Dental Sciences, University of Birmingham. *"Cefiderocol is active against all the critical pathogens that are most concerning to the World Health Organization so will be a much-needed option for clinicians treating some of the most severe Gram-negative infections."*

Cefiderocol

Cefiderocol is the world's first siderophore cephalosporin antibiotic with a novel mechanism of entry through the outer membrane of Gram-negative pathogens by using the bacteria's own iron uptake system to gain cell entry, acting like a Trojan horse. 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.[10] 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.[4]

Carbapenem resistance (CR) in Gram-negative bacteria is due to three main mechanisms:

- Beta-lactamases which cause enzymatic breakdown of beta-lactams

- Changes in porin channels (through mutations and decrease in number) through which beta-lactams and other antibiotics diffuse into cells,
- Overexpression of efflux pumps which occurs post-exposure and pumps antibiotics out of cells

As a result of its novel structure and mechanism of cell uptake, cefiderocol can overcome these three major mechanisms of CR.

"This approval represents another significant milestone in Shionogi's ongoing commitment to develop medicines that help fight these life-threatening infections in patients for whom limited, or no alternative treatment options exist," said Takuko Sawada, Director of the Board, Executive Vice President. *"Cefiderocol's novel mechanism of cell entry is like a Trojan horse; it exploits the bacteria's own iron uptake transporters to effectively enter the bacterial cell, which allows it to overcome the three major mechanisms of carbapenem-resistance in Gram-negative bacteria."*

Resistant Gram-negative infections

The increasing resistance of many infections caused by Gram-negative bacteria to existing therapies, including carbapenem-resistant Enterobacterales and non-fermenting species such as *P. aeruginosa, A. baumannii,* and *S. maltophilia*, makes them difficult to treat and results in high mortality rates.[11] The World Health Organization have identified carbapenem-resistant strains of Enterobacterales, *P. aeruginosa* and *A. baumannii* as the top priority in the research and development of new antibiotics.[2] Cefiderocol is the first antibiotic to address all three major mechanisms of carbapenem-resistance and is an important new treatment option to address this urgent unmet need.

As a result of COVID-19 some ventilated patients with viral pneumonia may develop secondary carbapenem-resistant Gram-negative bacterial infections. Similar to nosocomial pneumonia patients with carbapenem-resistant Gram-negative infections, Cefiderocol may be a considered as a treatment option.

About Antimicrobial Resistance

Antimicrobial resistance (AMR) is a major health burden which urgently needs to be addressed. In Europe about 25,000 patients die from an infection with multidrug-resistant bacteria every year[5]. Infections caused by carbapenem-resistant Gram-negative bacteria are often associated with a high mortality rate[12]. If no action is taken, antibiotic resistance is predicted to kill 10 million people every year by 2050, at a cumulative cost to global economic output of 100 trillion USD.[13]

About cefiderocol access

Shionogi is committed to making Cefiderocol available as quickly as possible in the European Economic Area, to adult patients (18 years or older) with infections due to aerobic Gram-negative bacteria and limited treatment options

Cefiderocol is commercially available in the U.S after approval by the FDA in 2019 under the brand name FETROJA® for patients 18 years of age or older who have limited or no alternative treatment options, for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis, caused by the following: susceptible Gram-negative microorganisms: *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa,* and *Enterobacter cloacae* complex.[14]

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.[15]

About Shionogi

Shionogi & Co., Ltd. is a 142-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 http://www.shionogi.co.jp/en/.
Shionogi B.V. is the European headquarters of Shionogi & Co., Ltd. For more information on Shionogi B.V., please visit www.shionogi.eu.

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.

FETCROJA SMPC: https://www.shionogi.eu/media/418054/ema-combined-h-4829-en.pdf

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