

FOR EUROPEAN MEDICAL AND PHARMA TRADE MEDIA ONLY

SHIONOGI RECEIVES POSITIVE CHMP OPINION FOR FETCROJA[®] (CEFIDEROCOL) FOR THE TREATMENT OF INFECTIONS DUE TO AEROBIC GRAM-NEGATIVE BACTERIA IN ADULT PATIENTS WITH LIMITED TREATMENT OPTIONS

- FETCROJA[®] (cefiderocol) has received a positive opinion from the CHMP for the treatment of infections due to aerobic Gram-negative bacteria in adult patients with limited treatment options¹
- This positive opinion was supported by the clinical data submitted by Shionogi from three key studies: CREDIBLE-CR, APEKS-cUTI and APEKS-NP¹
- As the application relied on the nonclinical data and the PK/PD package (including in vitro data), determination of a non-clinical PK/PD target and PTA simulations using clinical PK data, were crucial to the application¹
- 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 bacteria², so new and effective treatment options are urgently needed
- 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 Enterobacterales^{3,4}

OSAKA, Japan and AMSTERDAM, NL, [2 March 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 Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has issued a positive opinion recommending the approval of FETCROJA[®] (cefiderocol), a new antibiotic for the treatment of infections due to aerobic Gram-negative bacteria in adult patients (18 years or older) with limited treatment options.¹

The positive CHMP opinion of cefiderocol was based on the nonclinical data package, including the PK/PD data package, and data from three clinical studies in complicated UTI, nosocomial pneumonia and critically ill patients with confirmed carbapenem-resistant infection.

“We are delighted with the positive CHMP opinion which marks an important milestone in the journey to approval for this innovative new antibiotic,” said Takuko Sawada., Director of the Board, Executive Vice President. “Cefiderocol has a unique mechanism of cell entry, exploiting the bacteria’s own iron uptake transporters to effectively enter the bacterial cell. This allows it to overcome the three major mechanisms of carbapenem-resistance in Gram-negative bacteria. If approved, cefiderocol will be an important new treatment option for patients with these particularly difficult to treat Gram-negative infections who have limited options available to them.”

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 selected multi-drug resistant bacteria every year². Infections caused by carbapenem-resistant Gram-negative bacteria are often associated with higher mortality compared to those involving other strains⁵. 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.⁶ If approved, cefiderocol will be the first antibiotic to address all three major mechanisms of carbapenem-resistance and will be an important new treatment option to address this urgent unmet need.

The European Commission will review the CHMP opinion and is expected to deliver its final decision later this year.

About FETCROJA[®] (cefiderocol)

FETCROJA 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, 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.⁷ 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.⁸ FETCROJA has also demonstrated *in vitro* activity against certain bacteria that contain very problematic resistant enzymes such as ESBLs, AmpC, serine- and metallo-carbapenemases.^{9,10} 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*, *Pseudomonas aeruginosa*, Enterobacterales, and *Stenotrophomonas maltophilia*.¹¹ The clinical significance of the *in vitro* data is unknown. FETCROJA has no clinically relevant activity against Gram-positive or anaerobic bacteria.

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.¹²

About 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*, means there is a critical need for new, effective therapies.^{13,14,15} There are an increasing number of Gram-negative pathogens resistant to multiple antibiotics, making them difficult to treat and resulting in high mortality rates.¹⁶ In the U.S., at least 2 million people are infected with antibiotic-resistant bacteria, and at least 23,000 people die as a result each year.¹⁷ In the EU, about 25 000 patients die from an infection with the selected multidrug-resistant bacteria every year.² 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.³

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 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.¹⁸

About Shionogi

Shionogi & Co., Ltd. is a 141-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.

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