FOR UK MEDICAL AND PHARMA TRADE MEDIA ONLY

SHIONOGI'S NOVEL ANTIBIOTIC, FETCROJA® (CEFIDEROCOL), HAS BEEN SELECTED BY UK'S NICE / NHSE&I AS PART OF AN ANTIMICROBIAL SUBSCRIPTION STYLE REIMBURSEMENT MODEL

- The National Institute for Health and Care Excellence (NICE) and the National Health Service England and Improvement (NHSE&I) have recognised the potential of Shionogi's innovative antibiotic, cefiderocol, and selected it for inclusion in this pilot reimbursement model which 'de-links' payment from volume of use
- Shionogi recognises the UK's leadership role in introducing this first fully 'delinked' pilot reimbursement model, which is an important step in making the market for novel antibiotics more predictable and sustainable; we strongly believe in the introduction of further suitable pull incentives in order to help stimulate the antimicrobial development pipeline
- Fetcroja® (cefiderocol) is indicated for the treatment of infections due to aerobic Gram-negative bacteria in adults with limited treatment options[1]
- Antimicrobial resistance (AMR) is a major health burden which results in over 700,000 deaths globally[2] and 5,000 deaths per year in the UK[3] from an infection with multidrug-resistant bacteria and this is predicted to kill 10 million people every year globally by 2050, unless action is taken[2]

OSAKA, Japan, AMSTERDAM, NL – December 21, 2020 - Shionogi & Co., Ltd. and its European subsidiary, Shionogi B.V. (hereafter "Shionogi"), today announce that NICE and NHSE&I have selected its innovative antibiotic, cefiderocol, for inclusion in a pilot subscription reimbursement model in the UK which 'de-links' payment from volume of use, thereby recognising its potential in treating multidrug resistant Gram-negative bacterial infections and its benefits to society and healthcare systems. This scheme is called the *UK Project for developing and testing an innovative model for the evaluation and purchase of antimicrobials*. Pull incentives such as this are an important step to help bring urgently needed new antibiotics to market.

The aim of this scheme, which was officially announced by Matt Hancock, Secretary of State for Health, at the World Economic Forum in January 2019, is to pilot a model that reimburses companies for

antimicrobials based on a health technology assessment of their value to the NHS, rather than the volumes used.[4] The selection process by NICE and NHSE&I was designed to favour products which meet a key need in the UK while also addressing disease areas of international importance, in particular those drugs which treat serious infections including blood stream infection (BSI), sepsis and hospital or ventilator acquired pneumonia (HAP & VAP). A range of factors, including degree of novelty, activity against the WHO critical priority pathogen list, surety of supply, the supplier's demonstrated commitment to antimicrobial and environmental stewardship and commitment to support surveillance were considered. As a next step, NICE will further assess cefiderocol in 2021, and implementation of the subscription-based payment is due to commence in April 2022[4].

"We are delighted that NICE and NHSE&I have recognised the important role of Shionogi and our novel antibiotic, cefiderocol, in the fight against antimicrobial resistance. Our bid was assessed according to a rigorous selection process, including novelty, activity against the most difficult to treat pathogens and serious infection, surety of supply and antimicrobial stewardship, and our company and our medicine met all these criteria," said Dr Mark Hill, MB, BS, MRCP, Global Head of Market Access, Shionogi. *"We look forward to working closely with NICE next year, and hope that their new value assessment methodology will allow the full the value of cefiderocol to be reflected."*

While developing antibiotics is a long, risky and costly process, commercialisation is also challenging. Once launched, there is often a low frequency of use driven by the need for stewardship to prevent resistance development. Low use leads to limited revenues, which in turn restricts continued commercialisation and new product research. As a result of these economic challenges, many large pharmaceutical companies are no longer active in the development and commercialisation of antibiotics, and several smaller biotech companies have filed for bankruptcy. Shionogi strongly supports the introduction of new incentives, funding and value assessment models for reimbursement to restore a viable commercial environment to address the economic challenge faced in bringing novel antibiotics to market.

"The UK has demonstrated its leadership position with the introduction of this pilot subscription reimbursement model, which aims to recognise the benefit of new antibiotics to society," commented Takuko Sawada, Executive Vice President, Shionogi. *"Shionogi feels this is an important step in making the market for new antibiotics more predictable and sustainable. We hope that it will set a positive precedent for further innovative payment mechanisms in the future."*

Antimicrobial resistance (AMR) is a major health burden which urgently needs to be addressed. There are 700,000 deaths globally[2], ~25,000 deaths per year in the EU[5] and 5,000 deaths in the UK[3] from an infection with multidrug-resistant bacteria. Infections caused by carbapenem-resistant Gram-negative bacteria are often associated with a high mortality rate.[6] If no action is taken, antibiotic resistance is predicted to kill 10 million people every year globally by 2050, at a cumulative cost to global economic output of 100 trillion USD[2].

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.[7],[8] 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.[9] 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.[10]

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.[11] In addition to entering cells by passive diffusion through porin channels[12], 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.[13] 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[11].

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[14]

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

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 outcomes 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.ema.europa.eu/en/documents/product-information/fetcroja-epar-product-information_en.pdf

For further information about this announcement please see: https://www.england.nhs.uk/blog/how-the-nhs-model-to-tackle-antimicrobial-resistance-amr-can-set-a-global-standard/

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