

SHIONOGI SIGNS AGREEMENT WITH NHS ENGLAND TO BEGIN AN INNOVATIVE SUBSCRIPTION PAYMENT MODEL FOR REIMBURSEMENT OF ITS ANTIBIOTIC, FETCROJA® (CEFIDEROCOL)

- Shionogi and NHS England have signed an agreement to begin an innovative subscription payment model for reimbursement of cefiderocol in England which ‘de-links’ payment from volume of use¹
- Shionogi recognises the UK’s leadership role in introducing the world’s first fully ‘delinked’ pilot reimbursement model; pull incentives like this are an important step in making the market for novel antibiotics more predictable and sustainable
- As a result of the unsustainable economic model for antimicrobials, many large pharmaceutical companies are no longer active in the development and commercialisation of these drugs and some small biotech companies have faced bankruptcy²
- Antimicrobial resistance (AMR) is a major health burden, which results in over 700,000 deaths globally³ and 5,000 deaths per year in England⁴ from infections with multidrug-resistant bacteria. AMR is predicted to result in 10 million deaths every year globally by 2050, unless action is taken³

OSAKA, Japan, AMSTERDAM, NL – June 15-16, 2022 - Shionogi & Co., Ltd. and its European subsidiary, Shionogi B.V. (hereafter "Shionogi"), today announced that Shionogi B.V. had signed an agreement with NHS England to begin an innovative subscription payment model reimbursement of Cefiderocol in England. In this model, companies are paid a fixed sum for antimicrobials based on a health technology assessment of their value to the NHS, rather than the volumes used.¹ Shionogi welcomes the introduction of pull incentives to help bring urgently needed new antibiotics to market.

The deal follows draft guidance from NICE issued in April, which recommended Cefiderocol within its marketing authorisation as an option to treat severe drug-resistant infections caused by Gram-negative bacteria. It also states that the drug should be reserved for difficult to treat resistant infections, where there are few alternative options, and can only be used either in the microbiology-directed (‘confirmed’) treatment setting, or as risk-based empiric treatment.⁵ NICE’s evaluation of Cefiderocol considered long-term population benefits, including the ‘insurance/diversity’ value of having additional antimicrobial treatment options available for the future, and the ‘enablement’ value associated with the continued

ability to provide other healthcare (such as chemotherapy and surgical procedures), that might otherwise be jeopardised by increasing antimicrobial resistance.⁵

Cefiderocol is one of two antimicrobial products selected and made available as part of the scheme by NICE and NHS England⁶ because they address key disease areas of unmet need in the UK and internationally, treating serious infections including blood stream infection (BSI), sepsis and hospital or ventilator acquired pneumonia (HAP & VAP). Shionogi has entered into an initial three-year contract, with the option to extend, by agreement, for up to another seven years, receiving an annual, value-based payment.⁵

“We are delighted that NICE and NHS England have recognised the important role of Cefiderocol as an option to treat some of the most serious multidrug-resistant infections and its value to healthcare systems and society,” said Mark Hill, SVP, Global Head of Market Access, Shionogi. *“Antimicrobial resistance is becoming a significant global threat and subscription-style schemes like this help to ensure that antibiotics are used to benefit patients who need them and according to effective stewardship principles to limit the potential development of resistance.”*

While developing antibiotics is a long, costly and uncertain process, commercialisation can also be 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.²

“The introduction of this first of its kind pilot subscription reimbursement model reinforces the UK’s leadership position in creating a more predictable and sustainable market for new antibiotics,” commented Takuko Sawada, Director and Executive Vice President, Shionogi. *“We hope that other countries will follow suit and introduce pull incentives to help address the challenges faced in bringing novel antibiotics to market.”*

Antimicrobial resistance (AMR) is a major health burden which urgently needs to be addressed. There are 700,000 deaths globally³, ~25,000 deaths per year in the EU⁷ and 5,000 deaths in England⁴ from infections with multidrug-resistant bacteria. Infections caused by carbapenem-resistant Gram-negative bacteria are often associated with a high mortality rate.⁸ If no action is taken, antibiotic resistance is

predicted to result in 10 million deaths every year globally by 2050, at a cumulative cost to global economic output of 100 trillion USD.³

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.^{9,10} 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.¹¹ Cefiderocol is the first antibiotic to address all three major mechanisms of carbapenem-resistance and is an important treatment option to address this urgent unmet need.¹²

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.¹³ In addition to entering cells by passive diffusion through porin channels¹⁴, 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.¹⁵ These mechanisms allow Cefiderocol 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.¹³

Carbapenem resistance (CR) in Gram-negative bacteria is due to three main mechanisms:¹⁶

- 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 cells¹⁷

As a result of its novel structure and mechanism of cell uptake,¹⁸ 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 companies¹⁹).

About Shionogi

Shionogi & Co., Ltd. is a 144-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

<https://www.medicines.org.uk/emc/product/11771/smpc#gref>

For further information about this announcement please see: <https://www.nice.org.uk/news/article/nice-reaches-important-milestone-in-the-uk-s-efforts-to-tackle-antimicrobial-resistance>

For further information, contact:

Shionogi UK contact

Jo Taylor

jo.taylor@shionogi.eu

Havas SO Media Contact

Nicola Lilley

Associate Director

+44 7717 187 538

Nicola.lilley@havasso.com

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