Shionogi, GARDP and CHAI announce landmark license and collaboration agreements to treat bacterial infections by expanding access to cefiderocol in 135 countries

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Shionogi & Co., Ltd. (Shionogi) and the Global Antibiotic Research and Development Partnership (GARDP) have today announced the execution of a license and technology transfer agreement and, with the Clinton Health Access Initiative (CHAI), a collaboration agreement that aim to significantly transform the landscape of access to antibiotics for countries around the world.

The agreements will provide access to cefiderocol, an antibiotic for the treatment of serious Gram-negative bacterial infections, which may be resistant to other antibiotic treatments. Cefiderocol was recently added to the World Health Organization (WHO) Model List of Essential Medicines and targets a number of Gram-negative WHO priority pathogens. It was approved by the European Medicines Agency in 2020 and, separately, by the U.S. Food and Drug Administration in 2019. Please refer to the detailed U.S. indications and Important Safety Information for cefiderocol found below.

This is the first license agreement for an antibiotic to treat serious bacterial infections between a pharmaceutical company and a non-profit organization driven by public health priorities. Under this agreement, GARDP will manufacture and commercialize cefiderocol through sub-licensees in a large range of countries that have delayed access (if any) to newer antibiotics. The license territory includes all low-income countries, most lower middle- and upper middle-income countries, and select high-income countries (135 countries total, almost 70% of countries worldwide). It includes a significant proportion of the world's population living in areas most affected by antibiotic resistance.

"Shionogi is proud to work on such an innovative license agreement with GARDP and CHAI to accelerate antibiotic access. Shionogi is committed to ensuring that cefiderocol is accessible worldwide as a potential treatment option for certain highly resistant Gram-negative infections," stated Takuko Sawada, Director and Executive Vice President, Senior Vice President of Integrated Disease Care Division, Shionogi & Co., Ltd.

Antibiotic resistance is a growing public health emergency. A recent study found that antibiotic resistance caused nearly 1.3 million deaths worldwide in 2019—almost double previous estimates.

"Too often, antibiotic resistance is presented as a problem for the future," said Manica Balasegaram, Executive Director of GARDP. "In fact, resistant bacterial infections are already costing lives and taking a heavy toll on health systems around the world. We can change that by supporting accelerated access to antibiotics in regions with the highest burden of resistance—that is, where antibiotic access is often neglected, and should be prioritized. Thanks to essential

support from our funding partners, and in collaboration with Shionogi and CHAI, GARDP is accelerating global access now, so that doctors and patients who urgently need antibiotics can get them. Antibiotic development and delivery go hand-in-hand in GARDP's efforts to fight antibiotic resistance."

Getting cefiderocol to patients in need will require overcoming a number of technical, legal, regulatory and economic barriers. Shionogi and GARDP will collaborate with CHAI, which has expertise working with the public and private sectors to reshape markets and introduce medicines in countries around the world.

"Appropriate diagnosis and treatment of bacterial infections, which would include access to innovative medications like cefiderocol, can improve the treatment of life-threatening infections," stated David Ripin, Chief Science Officer and Executive Vice President of Infectious Diseases at CHAI. "CHAI is excited to be a part of this partnership that will ensure that this innovative antibiotic is affordable and available to patients when and where they need it."

The collaboration agreement includes provisions to work with ministries of health and other experts to strengthen hospital-based stewardship programs that ensure appropriate use. These provisions are especially important to avoid fueling resistance to cefiderocol.

According to Kamini Walia, Senior Scientist and Program Officer of AMR at the Indian Council of Medical Research, "New therapeutic options are urgently needed for treating highly resistant infections in Indian patients. Making cefiderocol available to appropriate Indian patients earlier than it was expected to hit Indian markets will be immensely beneficial in treating patients. However, there is need to practice strict stewardship around use of this drug to prevent its misuse and overuse." India is one of the many countries that may benefit from the license and collaboration agreements.

This project has a broader purpose to pave the way for antibiotic access more generally. Shionogi and GARDP have agreed to publish their innovative license agreement, which may serve as a new baseline for similar agreements in the future. The license and collaboration agreements also offer a dynamic and promising collaborative approach to antibiotic access. By bringing together key actors from the private and non-profit sectors, this project may help overcome barriers so that cefiderocol reaches patients in need.

About the partners

Shionogi
Shionogi & Co., Ltd. is a leading global research-driven pharmaceutical company based in Japan 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 has discovered and developed novel medicines for HIV, influenza and antimicrobial resistance and currently markets products in several therapeutic areas including anti-infectives with the first siderophore cephalosporin (cefiderocol). Other therapeutic areas, and the focus of the company's pipeline, include CNS/psychoneurological diseases, oncology and pain. For more information on Shionogi & Co., Ltd., visit https://www.shionogi.com/global/en/. Shionogi Inc. is the U.S. subsidiary of Shionogi & Co., Ltd. based in New Jersey. For more information on Shionogi Inc., please visit https://www.shionogi.com/us/en/. Shionogi B.V. is the European headquarters of Shionogi & Co., Ltd. For more information on Shionogi B.V., please visit www.shionogi.eu.

The Global Antibiotic Research and Development Partnership (GARDP)
GARDP is a Swiss not-for-profit organization developing new treatments for drug-resistant infections that pose the greatest threat to health. GARDP was created in 2016 by the World Health Organization (WHO) and the Drugs for Neglected Diseases *initiative* (DND*i*) and legally founded in 2018 to ensure that everyone who needs antibiotics receives effective and affordable treatment, no matter where they live. It is developing new treatments to fight drug-resistant infections, with a focus on sexually transmitted infections, sepsis in newborns, and infections in hospitalized adults and children. GARDP is working with over 60 partners in more than 20 countries. Its work is funded by the governments of Australia, Germany, Japan, Luxembourg, Monaco, Netherlands, South Africa, Switzerland, United Kingdom and the Canton of Geneva, as well as Médecins Sans Frontières and private foundations. GARDP is registered under the legal name GARDP Foundation. https://gardp.org/

The Clinton Health Access Initiative
The Clinton Health Access Initiative, Inc. (CHAI) is a global health organization committed to saving lives and reducing the burden of disease in low- and middle-income countries. We work with our partners to strengthen the capabilities of governments and the private sector to create and sustain high-quality health systems that can succeed without our assistance.
https://www.clintonhealthaccess.org/

Other partners
GSK
GSK collaborated with Shionogi to develop cefiderocol, and both companies are committed to support access to medicines for patients living in low- and middle-income countries (LMICs). To help make cefiderocol affordable and available to more people through the Shionogi collaboration with GARDP and CHAI, GSK will forego its royalties from sales in LMICs.

Ping An
Ping An Insurance (Group) Company of China, Ltd. is collaborating with Shionogi to develop cefiderocol in Asia through their joint venture companies, and both companies are committed to support access to medicines for patients living in low- and middle-income countries (LMICs). To help make cefiderocol affordable and available to more people in Asia, Ping An Insurance (Group) Company of China, Ltd. supports the Shionogi collaboration with GARDP and CHAI.

About cefiderocol
Cefiderocol for injection is the first and only siderophore cephalosporin antibiotic for the treatment of serious Gram-negative infections. It has 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. 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. Cefiderocol has also demonstrated *in vitro* activity against certain bacteria that contain problematic resistant enzymes such as ESBLs, AmpC, and serine- and metallo-carbapenemases. Data from multinational surveillance studies for cefiderocol demonstrated potent *in vitro* activity against a wide spectrum of Gram-negative pathogens including carbapenem-resistant *A. baumannii* complex*, P. aeruginosa*, Enterobacterales and *S. maltophilia*. The clinical significance of the *in vitro* data is unknown. Cefiderocol has no clinically relevant *in vitro* activity against most Gram-positive bacteria and anaerobic bacteria.

EUROPA INDICATIONS

Fetcroja is indicated for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options. Consideration should be given to official guidance on the appropriate use of antibacterial agents. Click here for the summary of product characteristics.

U.S. INDICATIONS

Fetroja® (cefiderocol) is indicated in patients 18 years of age or older for the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis caused by the following susceptible Gram-negative microorganisms: *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa*, and *Enterobacter cloacae* complex.

Fetroja is indicated in patients 18 years of age or older for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, caused by the following susceptible Gram-negative microorganisms: *Acinetobacter baumannii* complex, *Escherichia coli, Enterobacter cloacae* complex, *Klebsiella pneumoniae, Pseudomonas aeruginosa*, and *Serratia marcescens*.

USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Fetroja and other antibacterial drugs, Fetroja should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Fetroja is contraindicated in patients with a known history of severe hypersensitivity to cefiderocol or other beta-lactam antibacterial drugs, or any other component of Fetroja.

WARNINGS AND PRECAUTIONS

Increase in All-Cause Mortality in Patients with Carbapenem-Resistant Gram-Negative Bacterial Infections

An increase in all-cause mortality was observed in patients treated with Fetroja as compared to best available therapy (BAT) in a multinational, randomized, open-label trial in critically ill patients with carbapenem-resistant Gram-negative bacterial infections (NCT02714595). Patients with nosocomial pneumonia, bloodstream infections, sepsis, or cUTI were included in the trial. BAT regimens varied according to local practices and consisted of 1 to 3 antibacterial drugs with activity against Gram-negative bacteria. Most of the BAT regimens contained colistin.

The increase in all-cause mortality occurred in patients treated for nosocomial pneumonia, bloodstream infections, or sepsis. The 28-Day all-cause mortality was higher in patients treated with Fetroja than in patients treated with BAT [25/101 (24.8%) vs 9/49 (18.4%), treatment difference 6.4%, 95% CI (-8.6, 19.2)]. All-cause mortality remained higher in patients treated with Fetroja than in patients treated with BAT through Day 49 [34/101 (33.7%) vs 10/49 (20.4%), treatment difference 13.3%, 95% CI (-2.5, 26.9)]. Generally, deaths were in patients with infections caused by Gram-negative organisms, including non-fermenters such as *Acinetobacter baumannii* complex, *Stenotrophomonas maltophilia*, and *Pseudomonas aeruginosa*, and were the result of worsening or complications of infection, or underlying comorbidities. The cause of the increase in mortality has not been established.

Closely monitor the clinical response to therapy in patients with cUTI and HABP/VABP.

Click here for Full U.S. Prescribing Information for Fetroja® (cefiderocol).