# License Agreement Overview

***Shionogi & Co., Ltd. (Shionogi) and GARDP have signed a license and technology transfer agreement and, with the Clinton Health Access Initiative (CHAI), a collaboration agreement, that together aim to improve affordable, sustainable and appropriate access to cefiderocol. The agreements are effective 15 June 2022.***

*"These agreements take us one step closer to a world in which low- and middle-income countries that need antibiotics to fight resistant infections have the same options as high-income countries."*

**Jennifer Cohn**
**Global Access Project Leader, GARDP**

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. The license territory includes all low-income countries, most lower middle- and upper middle-income countries, and select high-income countries. Shionogi and GARDP have agreed to publish their innovative license agreement, which may serve as a new baseline for similar agreements in the future.

In addition, the three-way collaboration agreement between Shionogi, GARDP and CHAI will help roll out cefiderocol, including quality assurance, generation of real-world best practices, and appropriate use. CHAI will provide its expertise in working with licensed manufacturers to accelerate affordable product manufacturing and provide input on market shaping for cefiderocol.

Cefiderocol is an antibiotic for the treatment of serious Gram-negative bacterial infections, which may be resistant to other antibiotic treatments. It was 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 US Food and Drug Administration in 2019. Please refer to the detailed US indications and Important Safety Information for cefiderocol found below.

# LICENSE AGREEMENT SUMMARY

Shionogi has granted GARDP a non-exclusive and sub-licensable license for cefiderocol in the territory outlined below ("Territory") to develop, register, manufacture and commercialize cefiderocol, all in accordance with the terms of the agreement.

## Territory technology transfer

The Territory covers 135 countries, almost 70% of countries worldwide, including countries with some of the highest burden of infections due to resistant pathogens for which cefiderocol is indicated.

The license agreement will include the payment of cost recoupment fees to Shionogi on net sales made in certain parts of the Territory:

- High-income countries: 9%
- Upper middle-income countries: 5%
- Lower middle-income countries: 0%
- Low-income countries: 0%

## Technology transfer and intellectual property

If a manufacturer requests a technology transfer, Shionogi will provide one technology transfer of its manufacturing process, including relevant know-how, to one manufacturing sub-licensee (or, if the manufacturers of the active pharmaceutical ingredient (API) and finished pharmaceutical product are different, then one technology transfer covering the complete development from API to finished pharmaceutical product, but to two different manufacturers).

In addition, Shionogi will provide access to documents and necessary rights of referral to enable product registrations at national regulatory bodies and at the WHO Prequalification Programme (PQ). Additional and subsequent sublicensees will be provided relevant technology transfer, including documentation, by either GARDP (including via a third party), CHAI, or the sublicensee that received the initial technology transfer.

## Stewardship

The license agreement requires that the manufactured licensed product be demonstrated to be quality-assured through approval by a stringent regulatory authority, i.e. WHO Prequalification Programme, or a regulatory authority that achieves WHO maturity level 3 or 4. Additional stewardship clauses will be agreed upon in sub-licensee agreements and as part of sublicense access plan developed with sub-licensees. In addition, stewardship activities and partnerships will be developed through collaboration activities.

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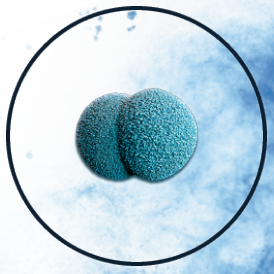
## List of countries included in Territory

| High Income | Upper Middle Income | | Lower Middle Income | | Low Income |
|---|---|---|---|---|---|
| Antigua | Albania | Maldives | Algeria | Mauritania | Afghanistan |
| Bahamas | Argentina | Marshall Isl. | Angola | Micronesia | Burkina Faso |
| Barbados | Armenia | Mauritius | Bangladesh | Mongolia | Burundi |
| Chile | Azerbaijan | Mexico | Belize | Morocco | Central African Republic |
| Nauru | Belarus | Moldova | Benin | Myanmar | Chad |
| Palau | Bosnia, Herz. | Montenegro | Bhutan | Nepal | Dem. People's Rep. of Korea |
| Seychelles | Botswana | Namibia | Bolivia | Nicaragua | Dem. Rep. of Congo |
| St Kitts | Brazil | N. Macadonia | Cabo Verde | Nigeria | Eritrea |
| Trinidad/Tobago | Colombia | Panama | Cambodia | Pakistan | Ethiopia |
| Uruguay | Costa Rica | Paraguay | Cameroon | Papua NG | Gambia |
| | Cuba | Peru | Comoros | Samoa | Guinea |
| | Dominica | Serbia | Congo, Rep. of | São Tomé | Guinea-Bissau |
| | Dominican Rep. | South Africa | Côte d'Ivoire | Senegal | Liberia |
| | Ecuador | St. Lucia | Djibouti | Solomon Isl. | Madagascar |
| | Eq. Guinea | St. Vincent | Egypt | Sri Lanka | Malawi |
| | Fiji | Suriname | El Salvador | Tanzania | Mali |
| | Gabon | Tonga | Eswatini | Tajikistan | Mozambique |
| | Georgia | Turkmenistan | Ghana | Timor-Leste | Niger |
| | Grenada | Tuvalu | Haiti | Tunisia | Rwanda |
| | Guatemala | Venezuela | Honduras | Ukraine | Sierra Leone |
| | Guyana | | India | Uzbekistan | Somalia |
| | Iraq | | Iran, Islamic Rep | Vanuatu | South Sudan |
| | Jamaica | | Kenya | Zambia | Sudan |
| | Jordan | | Kiribati | Zimbabwe | Syrian Arab Republic |
| | Kazakhstan | | Kyrgyz Rep. | | Togo |
| | Lebanon | | Lao PDR | | Uganda |
| | Libya | | Lesotho | | Yemen |



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## 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, 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.

### US 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 US Prescribing Information for cefiderocol.