

# Towards investigation, development and introduction of cefiderocol in children: product brief

Cefiderocol is the first siderophore cephalosporin antibiotic for serious gram-negative bacterial infections that may be resistant to other antibiotic treatments. It inhibits bacterial enzymes responsible for cell-wall synthesis.

## Activity against WHO critical pathogens

Cefiderocol is active against several WHO priority pathogens, such as carbapenem-resistant Enterobacterales (including *Klebsiella* species), *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. It maintains activity against Enterobacterales isolates that produce metallo-beta lactamases for which few other options exist, which is the most prevalent genotypic type of carbapenem resistance in many regions (such as India).

Cefiderocol has little or no activity against most gram-positive organisms and anaerobes. Alternative antibacterial medicinal products should be used when these pathogens are known or suspected to be contributing to the infectious process (1).

## Formulation and administration

1 g (as sulfate tosylate) in a vial to be stored refrigerated at 2–8°C, protected from light.

To administer by intravenous infusion over 3 hours (at a dose of 2 g every 2 hours) usually for 7–14 days (treatment duration varies according to indication and should be as short as possible).

## Regulatory approvals

**2019:** Approved by the United States Food and Drug Administration (US FDA) for treating people 18 years and older with complicated urinary tract infections (cUTI) and hospital-acquired or ventilator-associated pneumonia.

**2020:** Approved by the European Medicines Agency (EMA) in 2020 for infections caused by gram-negative organisms among people 18 years and older with limited treatment options (broader indication than approval by the United States Food and Drug Administration).

## WHO model list of essential medicines

Included since 2020 on the WHO Model List of Essential Medicines as a reserve group antibiotic: reserved for confirmed or suspected infections caused by multidrug-resistant (MDR) organisms. Reserve group antibiotics should be treated as last-resort options.

# What about children?

Despite a significant decline in deaths among children younger than five years globally in the past three decades, preventable and treatable infectious diseases remain the leading cause of death in this age group (2). Bacterial infections, especially pneumonia, neonatal sepsis and gastrointestinal infections, are the main cause of infectious mortality among children younger than five years worldwide. This problem is further exacerbated by the global rise of antimicrobial resistance (AMR).

The WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) report confirms that antibacterial resistance is on the rise (3), specifically in low- and middle-income countries, causing significant mortality and morbidity (2). Vulnerable populations such as children and neonates are disproportionately affected by antibiotic-resistant infections in these countries, with pneumonia and bloodstream infections among the major causes of mortality among children younger than five years. About 30% of newborns with sepsis die from bacterial infections resistant to first-line antibiotics (4).

New antibacterial treatments are thus urgently needed, and children should not be left behind, in accordance with the global call enshrined in

the Sustainable Development Goals that puts the world's most vulnerable and marginalized people – including children – at the top of the global health agenda.

Setting priorities is a necessary first step to enable a targeted approach to research on and development of medicines and formulations to treat a range of diseases among children. Developing a priority drug portfolio of the most needed products and formulations for children is essential to streamline researchers' and supplier's efforts and resources around specific products, dosage forms and formulations that address the most urgent needs for children. This is especially important since the market for paediatric medicines is often small and/or fragmented, resulting in limited volumes with potential market failures.

In November–December 2022, WHO undertook a PAediatric Drug Optimization (PADO) exercise for antibiotics to identify antibiotics with an approved indication for children for which age-appropriate formulations are missing that need to be given priority for development (PADO priority list) and pipeline or approved antibiotics without an indication for children to be given priority for further investigation and development for children (PADO watch list) (5).



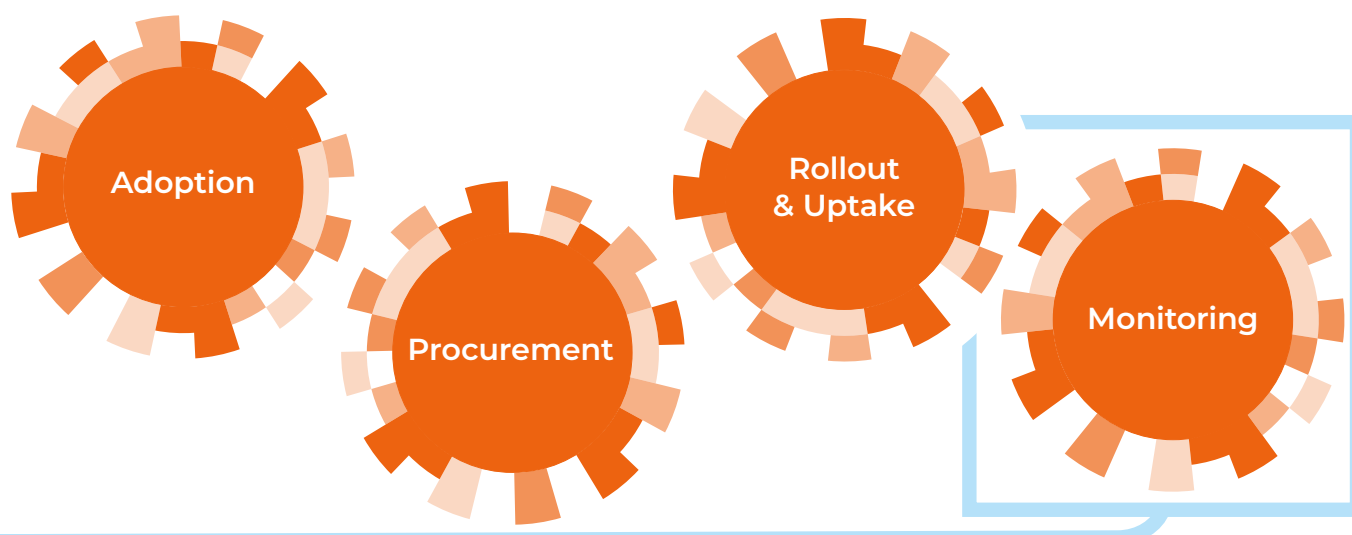
Cefiderocol was included in the PADO priority list because of its efficacy against multiple pathogens in the WHO bacterial priority pathogens list, its favourable resistance and cross-resistance profile and considering that clinical trials involving children are ongoing.

The priority-setting exercise considered several factors, including the potential public health impact for treating key clinical infections with the highest mortality and morbidity among neonates and other children, the most likely causative pathogens among neonates and other children and the most common phenotypic and genotypic resistance patterns. Other considerations included whether intravenous and/or oral administration is required and whether unique children-specific toxicity has been identified or the toxicity profile already defined in the adult population is of concern for

children. The epidemiology and disease burden associated with AMR among children varies between high- and low-income settings as well as within settings, and considering this variation has also been deemed fundamental.

EMA and the US FDA have both requested studies including children from birth to younger than 18 years to inform a potential extension of indication to children and neonates. However, the study designs and target populations requested in Europe and in the United States of America differ (Table 1). As a result, three different studies shall be performed highlighting the need for streamlined pediatric pathways.

In 2017, a paediatric investigation plan (PIP) was submitted to EMA to study cefiderocol among neonates and children for infections caused by aerobic gram-negative bacteria among children with limited therapeutic options (6). The paediatric investigation plan includes a juvenile toxicity study, the PEDI-CEFI study, as well as extrapolation and modelling and simulation studies.



The PEDI-CEFI study [NCT04335539] sponsored by Shionogi & Co., Ltd was a Phase 2, open-label, single arm study with the aim to assess the safety, tolerability and pharmacokinetics (PK) of single and multiple doses of cefiderocol in hospitalized pediatric participants. The study included 54 participants, from four age group cohorts from three months to less than 18 years of age and was completed in April 2023.

The APEKS-PEDI study [NCT04215991], which was designed and implemented to accommodate US FDA requirements, is a Phase 2, open-label, randomized, multicentre, active-controlled trial to evaluate the PK, safety and tolerability of cefiderocol among children from three months to younger than 18 years with cUTI. The dose for this study for children three months to younger than 12 years will be determined by the data from a single-dose, non-comparative study assessing the PK of cefiderocol among children from three months to younger than 12 years with suspected or confirmed gram-negative infections.

The study aims to enrol 82 participants at 19 sites (all currently active, 79% enrolment status as of October 2023). Three sites in Ukraine could no longer enrol because of the armed conflict and thus, two sites in Georgia and one in the USA were added. The study is expected to be completed in 2024.

A neonatal safety and PK study (NEO-CEFI) sponsored by Shionogi & Co, Ltd is expected to open for enrolment in the fourth quarter of 2023 in 17 sites, with expected completion at the end of 2024. The study is an open-label, single-arm non comparative study to evaluate PK, safety and tolerability of single dose and multiple doses of cefiderocol in hospitalized infants from birth to younger than three months with suspected or confirmed infections cause by aerobic gram-negative bacteria. The dose of cefiderocol differs according to the gestational and postnatal age of the infant (Table 1). Twelve single-dose participants will be initially enrolled and then, once assessed, a further 28 multiple-dose participants will be enrolled.



**TABLE 1. ONGOING AND PLANNED PAEDIATRIC STUDIES ON CEFIDEROCOL FOR EXPANDING EMA AND US FDA INDICATIONS**

	SEEKING REGULATORY APPROVAL AT	CURRENT INDICATION (APPLIES TO A POTENTIAL LABEL UPDATE FOR CHILDREN)	DESIGN	POPULATION (AGE)	DOSE	ESTIMATED ENROLMENT (NUMBER OF PARTICIPANTS)	STATUS	EXPECTED COMPLETION
PEDI-CEFI	EMA	Infections caused by gram-negative organisms among people 18 years and older with limited treatment options.	Open-label, single-arm study	3 months to <18 years	<34 kg: 60 mg/kg IV ≥34 kg: 2000 mg IV	54	Completed	Completed (April 2023)
APEKS-PEDI	US FDA	cUTI and HAP/VAP among people aged 18 years and above	Open-label, randomized, multicentre, active-controlled trial	3 months to <18 years	<34 kg: 60 mg/kg IV ≥34 kg: 2000 mg IV	85	Enrolling (75%)	Q2–Q3 2024
NEO-CEFI	EMA and US FDA	-	Open-label, single-arm on-comparative study	<3 months with suspected or confirmed infections cause by aerobic gram-negative bacteria.	Gestational age <32 weeks and postnatal age from birth to <2 months: 30 mg/kg. less than two months old: 30 mg/kg  Gestational age <32 weeks and postnatal age of 2–<3 months: 40 mg/kg.  Gestational age of 32 weeks and postnatal age from birth to less than <2 months: 40 mg/kg  Gestational age ≥32 weeks or postnatal age of 2–<3 months: 60 mg/kg	40	Open for enrolment, Oct 2023	Q4 2024

cUTI: complicated urinary tract infections; EMA: European Medicines Agency; HAP/VAP: hospital-acquired and ventilator-associated pneumonia; IV: intravenous; kg: kilogram; mg: milligram; Q: quarter; US FDA: United States Food and Drug Administration.

# Ensuring access for everyone in need

Ensuring optimal and equitable access to antibiotics worldwide and their appropriate use to avoid the emergence of resistance are cornerstones of any public health-driven approach towards achieving universal health coverage. However, several barriers exist that have been hindering access to antibiotics, especially in low- and middle-income countries, including unpredictable, fragmented markets, with unclear or limited volumes, inadequate and vulnerable supply, insufficient distribution and lack of plans and funding for introducing new products.

In June 2022, the Global Antibiotic Research and Development Partnership (GARDP) signed an innovative licence and technology transfer agreement with Shionogi & Co., Ltd to expand and accelerate access to cefiderocol. This is the first licensing agreement for an antibiotic for serious bacterial infections between a pharmaceutical company and a non-profit organization driven by public health priorities (7).

The technology transfer includes sharing details about the manufacturing process, including relevant know-how, to one manufacturing sub-licensee (or, if the manufacturers of the active pharmaceutical ingredient and finished pharmaceutical product are different, then one technology transfer covering the complete development from active pharmaceutical ingredient to finished pharmaceutical product but to two different manufacturers). In addition, Shionogi & Co., Ltd will provide access to documents and necessary rights of referral to enable product registration at national regulatory bodies and prequalification by the WHO Prequalification Unit. Indeed, the licensing agreement requires that the manufactured licence product be demonstrated to be quality assured: prequalified by WHO or approved by a regulatory authority that achieved maturity level

3 or 4 and is listed as a WHO listed authority. A first invitation to manufacturers (expression of interest) for the evaluation of their product intended for MDR bacterial infections by the WHO Prequalification Unit was published in March 2023 and includes cefiderocol (8).

Additional and subsequent sublicensees will be provided relevant technology transfer, including documentation, by either GARDP (including via a third party), Clinton Health Access Initiative (CHAI) or the sublicensee that received the initial technology transfer.

The licence covers a wide geographical territory, including all low-income countries, most lower-middle- and upper-middle-income countries and select high-income countries, for a total of 135 countries (almost 70% of countries worldwide), including much of the world's population living in areas most affected by antibiotic resistance, where introducing cefiderocol would have the highest impact.

In parallel, GARDP also signed a collaboration agreement with CHAI to support the roll-out of cefiderocol, including quality assurance, generating real-world data and best practices for new antibiotic introduction, market shaping initiatives for cefiderocol and appropriate use.

In May 2023, GARDP announced a collaboration with the Stop TB Partnership Global Drug Facility on a pilot of pooled procurement for GARDP products, including cefiderocol.



# What's next?

## Funding priority interventions

### Cefiderocol...

- Accelerate the development, approval and introduction of cefiderocol for people of all ages, including children and neonates.
- Improve the evidence base for the optimal use of cefiderocol in neonates and children with severe infections caused by MDR pathogens, including its impact on mortality and morbidity, toxicity, resistance and health economic outcomes to inform future technology appraisal and country level implementation.
- Ensure that cefiderocol can be supplied at an affordable price, including by studying and executing improved manufacturing processes
- Carry out additional stability studies on the current formulation of cefiderocol.
- Leverage innovative study designs for timely approval of paediatric indications, minimizing off-label use competing with recruitment for clinical trials involving children.
- Ensure a suitable profile of newly developed antibiotics in terms of shelf-life and stability, to facilitate their introduction and uptake, especially in low- and middle-income countries.
- Establish sustainable, affordable and equitable access to newly developed antibiotics worldwide, such as the innovative licence and technology transfer agreement signed by GARDP and Shionogi & Co., Ltd for cefiderocol.
- Support countries in preparing for the uptake of new interventions as part of the public health approach that should be undertaken when introducing new antibiotics.

### ...and beyond

- Map out and support innovative introduction pathways for reserve antibiotics to ensure rapid access and appropriate use.
- Increase funding of research and development for new antibiotics to tackle AMR as a public health threat, especially in the context of neonatal sepsis and other severe bacterial infections.
- Initiate paediatric studies for critical products identified by PADO as early as possible in the development process.
- Assure the availability of suitable point-of-care diagnostics to significantly improve treatment outcomes by providing information about which antibiotic to use and avoiding unnecessary or incorrect use, reducing total antibiotic consumption and securing access in the long term (9).

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