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In vitro potency of ceftibuten with xeruborbactam against β-lactamase-producing isolates of Enterobacterales (ENT) from the SENTRY global surveillance programme

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SHIONOGI

Existing unmet need

- Existing **oral antibiotics are often ineffective**
- Transition ("step-down") of patients to **oral therapy** is an integral part of **antibiotic stewardship practice**

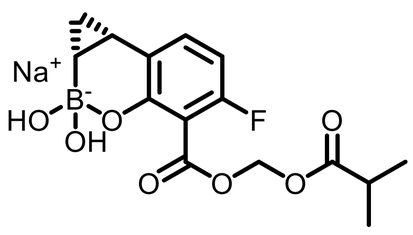
Limited oral options

- **Third-generation cephalosporins**: ESBL-mediated resistance
- **Fluoroquinolones**: resistance, safety concerns

A convenient oral option is important for patients

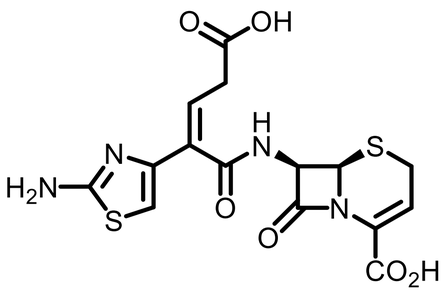
- **"Stay-home"** – Avoids hospitalization and infusion centers
- **"Go-home"** – IV-to-oral step-down therapy for early discharge

Ceftibuten-Xeruborbactam Prodrug For Oral Administration



Xeruborbactam prodrug

- Xeruborbactam is a potent inhibitor of numerous serine β-lactamases from molecular classes A, C and D and metallo-β-lactamases (from molecular class B1)
- Xeruborbactam prodrug has 100% oral bioavailability in humans



Ceftibuten

- 3rd generation cephalosporin with increased stability to some β-lactamases (KPC, CTX-M). Less impact of efflux and porin mutations compared to other β-lactams
- High oral bioavailability in humans due to active transport without the need for a prodrug

Objectives and Methods

➢ Objective: To determine the *in vitro* potency of ceftibuten-xeruborbactam and comparator agents against recent β-lactamase-producing isolates of Enterobacterales.

➢ Isolates: 20,671 isolates of Enterobacterales were collected during 2021–2022 in the SENTRY programme worldwide. 3,472 β-lactamase-positive isolates were identified based of β-lactam susceptibility profiles and subsequent whole-genome sequencing.

- *Escherichia coli* and *Klebsiella pneumoniae* isolates displaying MIC values ≥2 mg/L for at least 2 of the following β-lactams: ceftazidime, ceftriaxone, aztreonam, or cefepime.
- *Enterobacter cloacae* species complex (herein *E. cloacae*) and *Citrobacter* spp. isolates displaying MIC values ≥16 mg/L for ceftazidime and/or ≥2 mg/L for cefepime.
- Enterobacterales isolates displaying elevated carbapenem (meropenem and/or imipenem) MIC results >1 mg/L; *Proteus mirabilis* or indole positive *Proteus* spp. were only included if their meropenem MIC was >1 mg/L.

Conclusions

- **Ceftibuten-xeruborbactam has a broad coverage against Enterobacterales, with activity against ESBL- and carbapenemase-producing isolates comparable or better than some IV agents.**
- **The *in vitro* potency and spectrum of ceftibuten-xeruborbactam warrants further clinical development.**

Results

Table 1. Comparison of Susceptibility of IV and Oral Antibiotics with Ceftibuten-Xeruborbactam per Pathogen

	Ceftibuten-xeruborbactam	Amoxicillin-clavulanic acid	Levofloxacin	Trimethoprim-sulfamethoxazole	Ceftazidime-avibactam	Meropenem
***Escherichia coli* (N=9051)**						
MIC_{90}	0.03	16	16	8	0.25	0.03
%S	99.6%	78.6%	74.1%	69.2%	99.8%	99.7%
***Klebsiella pneumoniae* (N=4318)**						
MIC_{90}	0.125	>32	16	8	0.5	2
%S	98.4%	70.0%	73.0%	67.4%	97.3%	90.6%
Other *Klebsiella* (*K. oxytoca*, 830; *K. aerogenes*, 653; *K. variicola*, 161) (N=1644)						
MIC_{90}	0.125	>32	0.25	0.25	0.5	0.03
%S	99%	52.2%	94.9%	94.1%	99.5%	99.3%
***Enterobacter cloacae* complex (N=1512)**						
MIC_{90}	0.5	>32	0.5	8	1	0.125
%S	97.4%	4.4%	90.9%	85.5%	97.9%	97.4%
***Serratia* spp. (*S. marcescens*, 1097) (N=1150)**						
MIC_{90}	0.125	>32	0.5	0.5	0.5	0.06
%S	99.9%	3.2%	91.1%	96.6%	99.7%	98.7%

- Only species demonstrating less than 100% of susceptibility to ceftibuten-xeruborbactam were included in the Table
- MIC_{90} values are expressed in mg/L
- Xeruborbactam tested at 4 mg/L; PK-PD breakpoint of ceftibuten = 2 mg/L with 600 mg BID dosage regimen
- Other breakpoints (CLSI): ≤8/4, amoxicillin-clavulanic acid; ≤8/4, ceftazidime-avibactam; ≤1, meropenem; ≤0.5, levofloxacin; ≤2/38, trimethoprim-sulfamethoxazole

• Ceftibuten-xeruborbactam (2/4 mg/L) inhibited >95% of Enterobacterales.

Table 2. Comparison of Susceptibility of IV and Oral Antibiotics with Ceftibuten-Xeruborbactam Against β-Lactamase Producing Pathogens (N=3471)

	Ceftibuten-xeruborbactam	Amoxicillin-clavulanic acid	Levofloxacin	Trimethoprim-sulfamethoxazole	Ceftazidime-avibactam	Meropenem
***Escherichia coli* (N=1573)**						
MIC_{90}	0.06	32	32	8	0.5	0.06
%S	97.9%	50.5%	26.7%	40.7%	98.8%	98%
***Klebsiella pneumoniae* (*K. pneumoniae*, N=1346; *K. oxytoca*, 21) (N=1367)**						
MIC_{90}	1	>32	>32	8	4	>32
%S	94.7%	20.8%	29.6%	16.5%	91.1%	69.2%
***Enterobacter cloacae* complex (N=427)**						
MIC_{90}	2	>32	8	8	2	2
%S	91.1%	0%	79.6%	71.4%	92.5%	93.9%
***Citrobacter* spp. (*C. freundii* complex, 94) (N=104)**						
MIC_{90}	0.25	>32	4	8	1	0.06
%S	100%	5.8%	77.9%	72.1%	100%	97.1%

- MIC_{90} values are in mg/L
- Xeruborbactam tested at 4 mg/L; PK-PD breakpoint of ceftibuten = 2 mg/L with 600 mg BID dosage regimen
- Other breakpoints (CLSI): ≤8/4, amoxicillin-clavulanic acid; ≤8/4, ceftazidime-avibactam; ≤1, meropenem; ≤0.5, levofloxacin; ≤2/38, trimethoprim-sulfamethoxazole

• Ceftibuten-xeruborbactam (2/4 mg/L) maintained high levels of activity against β-lactamase-producing Enterobacterales.

Table 3. Comparison of Susceptibility of IV and Oral Antibiotics with Ceftibuten-Xeruborbactam per β-Lactamase

	Ceftibuten-xeruborbactam	Amoxicillin-clavulanic acid	Levofloxacin	Trimethoprim-sulfamethoxazole	Ceftazidime-avibactam	Meropenem
Class A ESBL (all CTX-M, 2252; CTX-M-15, 1630; no carbapenemase-producing CRE) (N=2236)						
MIC_{50}/MIC_{90}	≤0.015/0.125	16/32	8/32	8/8	0.125/0.5	0.03/0.06
%S	99.2%	45.8%	13%	28.6%	92.6%	98.3%
Plasmidic Class C (CMY, 161; DHA, 62; MIR, 12) (N=234)						
MIC_{50}/MIC_{90}	0.06/0.5	>32/>32	0.5/32	0.25/8	0.125/1	0.03/0.125
%S	95.3%	13%	60.3%	56%	99.6%	97%
Class D (OXA-1/OXA-30, 993; no carbapenemase-producing CRE) (N=995)						
MIC_{50}/MIC_{90}	≤0.015/0.125	16/32	8/32	8/8	0.25/0.5	0.03/0.06
%S	99.1%	6%	15.4%	22.6	100%	97.5%
KPC (N=246)						
MIC_{50}/MIC_{90}	0.125/0.5	32/>32	16/>32	8/8	1/4	32/>32
%S	99.2%	0%	12.6%	22%	98%	11.8%
OXA-48-like (N=111)						
MIC_{50}/MIC_{90}	0.125/1	32/>32	32/>32	8/8	1/2	16/>32
%S	98.2%	0%	11.7%	15.3%	100%	33.3%
Carbapenemase-negative CRE (N=122)						
MIC_{50}/MIC_{90}	0.5/32	>32/>32	4/>32	8/8	1/8	4/32
%S	72.1%	0%	36.9%	43.4%	91%	27.9%
MBL (NDM, 143; VIM, 21; IMP, 5) (N=171)						
MIC_{50}/MIC_{90}	4/>32	>32/>32	16/>32	8/8	>32/>32	>32/>32
%S	43.9%	0.6%	15.8%	18.1%	4.1%	9.4%

- MIC_{50} and MIC_{90} values are expressed in mg/L
- Xeruborbactam tested at 4 mg/L; PK-PD breakpoint of ceftibuten = 2 mg/L with 600 mg BID dosage regimen
- Other breakpoints (CLSI): ≤8/4, amoxicillin-clavulanic acid; ≤8/4, ceftazidime-avibactam; ≤1, meropenem; ≤0.5, levofloxacin; ≤2/38, trimethoprim-sulfamethoxazole

• Ceftibuten-xeruborbactam (2/4 mg/L) maintained high levels of activity against Enterobacterales carrying ESBLs, plasmidic Class C, Class D, KPCs, and OXA-48-like enzymes.

- **A reduced activity was noted against the small subset of carbapenemase-negative or MBL-producing Enterobacterales.**

Acknowledgements

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