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Antimicrobial Activity of Cefepime in Combination with Taniborbactam (formerly VNRX-5133) Against Clinical Isolates of Enterobacterales from Europe Collected from 2018-2020 Surveillance

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INTRODUCTION

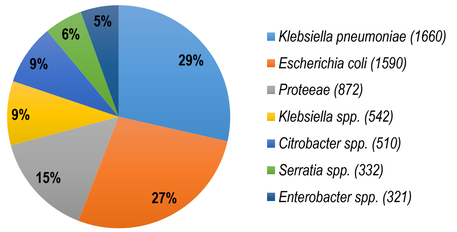
Taniborbactam, (formerly VNRX-5133), is a novel cyclic boronate-based broad-spectrum β-lactamase inhibitor with potent and selective direct inhibitory activity against both serine- and metallo-β-lactamases (Ambler Classes A, B, C and D). Taniborbactam greatly enhances the activity of cefepime against many difficult to treat organisms, including cephalosporin- and carbapenem-resistant Enterobacterales and *Pseudomonas aeruginosa*. In this study, we evaluated the in vitro activity of the investigational combination cefepime-taniborbactam and comparator agents against recent clinical isolates of Enterobacterales collected in Europe during 2018-2020 surveillance.

MATERIALS & METHODS

MICs of cefepime with taniborbactam fixed at 4 mg/L (FTB) and comparators were determined following CLSI M07-A11 guidelines [1] against 5,817 Enterobacterales (Figure 1). Quality control (QC) testing was performed each day of testing as specified by the CLSI [1, 2]. Isolates were from community and hospital infections collected from 113 sites in 24 European countries in 2018-2020 (Figure 2). Isolates were sourced from (n/percent of total): respiratory tract infections (2,143/36.8%), urinary tract infections (1,238/21.3%), intraabdominal infections (1,079/18.5%), bloodstream infections (939/16.1%), skin/soft tissue infections (417/7.2%), and unknown (1/<0.1%). Avibactam was tested at a fixed concentration of 4 mg/L in combination with ceftazidime, tazobactam was tested at a fixed concentration of 4 mg/L in combination with ceftolozane and piperacillin, and vaborbactam was tested at a fixed concentration of 8 mg/L in combination with meropenem. Resistant phenotypes were based on 2021 EUCAST breakpoints v11.0 [3]. As cefepime-taniborbactam breakpoints have not yet been established, the provisional non-resistant breakpoint of ≤8 mg/L was considered for comparative purposes. A set of 408 Enterobacterales with meropenem MIC ≥4 mg/L (n=227) or with cefepime/ceftazidime MIC ≥2 mg/L (n=181) was evaluated for the presence of MBL, KPC, ESBL, and OXA-48 group genes via PCR and Sanger sequencing. Eighteen isolates with cefepime-taniborbactam MIC values of ≥16 mg/L were interrogated by whole genome sequencing (WGS).

RESULTS

Figure 1. Distribution of 5,817 Enterobacterales isolates by species



Klebsiella spp. consist of (n): *K. oxytoca* (378); *K. aerogenes* (162); *K. variicola* (2)
Proteeae consist of (n): *Morganella morganii* (182); *Proteus mirabilis* (321); *P. vulgaris* (208); *Providencia alcalifaciens* (1); *P. rettgeri* (65); *P. stuartii* (94); *Providencia* sp. (1)
Serratia spp. consist of (n): *S. fonticola* (1); *S. liquefaciens* (22); *S. marcescens* (264); *S. rubidaea* (2); *S. ureilytica* (11); *Serratia* sp. (22)
Citrobacter spp. consist of (n): *C. amalonaticus* (2); *C. braakii* (30); *C. farmeri* (2); *C. freundii* (302); *C. koseri* (174)
Enterobacter spp. consist of (n): *E. asburiae* (17); *E. cloacae* (257); *E. cloacae* complex (34); *E. kobei* (7); *E. ludwigii* (4); *E. xiangfangensis* (1))

Figure 2. Distribution of 5,817 Enterobacterales isolates by country of isolation

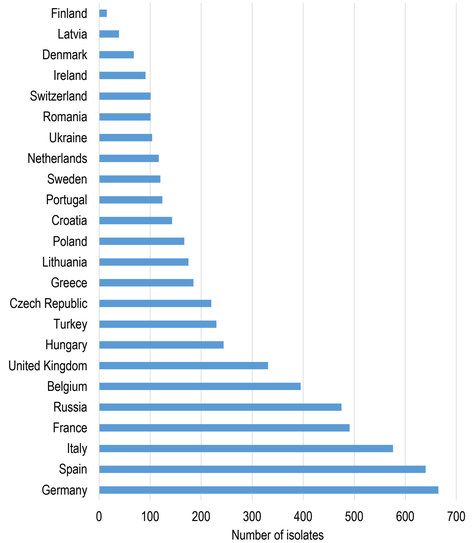


Table 1. *In vitro* activity of cefepime-taniborbactam and comparator agents against 5,817 Enterobacterales

Phenotype (n)	Antimicrobial	%S	%I	%R	MIC_{50}	MIC_{90}	Range
Enterobacterales (5,817)	Cefepime-taniborbactam	99.6	--	0.4[a]	0.06	0.25	≤0.008 - >16
	Cefepime	75.4	4.2	20.4	≤0.25	>16	≤0.25 - >16
	Ceftazidime	69.6	4.7	25.7	0.5	>16	≤0.03 - >16
	Ceftazidime-avibactam	98.0	--	2.0	≤0.12	0.5	≤0.12 - >16
	Ceftolozane-tazobactam	86.1	--	13.9	0.5	8	≤0.25 - >8
	Gentamicin	83.1	--	16.9	0.5	>16	≤0.12 - >16
	Levofloxacin	70.9	3.7	25.4	0.06	>8	≤0.004 - >8
	Meropenem	94.6	1.3	4.1	0.03	0.12	≤0.004 - >64
	Meropenem-vaborbactam	97.7	--	2.3	≤0.06	0.12	≤0.06 - >16
	Piperacillin Tazobactam	78.2	--	21.9	≤4	>128	≤4 - >128
Cefepime-NS (1,433)	Cefepime-taniborbactam	98.4	--	1.6	0.12	2	0.015 - >16
	Cefepime	0.0	17.0	83.0	>16	>16	2 - >16
	Ceftazidime	5.2	7.5	87.3	>16	>16	0.06 - >16
	Ceftazidime-avibactam	92.0	--	8.0	0.25	4	≤0.12 - >16
	Ceftolozane-tazobactam	52.7	--	47.3	2	>8	≤0.25 - >8
	Gentamicin	46.8	--	53.2	16	>16	≤0.12 - >16
	Levofloxacin	22.8	6.6	70.6	>8	>8	0.015 - >8
	Meropenem	78.8	4.8	16.4	0.06	32	≤0.004 - >64
	Meropenem-vaborbactam	90.7	--	9.4	≤0.06	8	≤0.06 - >16
	Piperacillin Tazobactam	38.9	--	61.1	32	>128	≤4 - >128
Meropenem-NS (313)	Cefepime-taniborbactam	93.9	--	6.1	1	8	0.03 - >16
	Cefepime	2.9	1.3	95.9	>16	>16	0.5 - >16
	Ceftazidime	3.2	0.6	96.2	>16	>16	0.5 - >16
	Ceftazidime-avibactam	68.1	--	32.0	2	>16	≤0.12 - >16
	Ceftolozane-tazobactam	1.6	--	98.4	>8	>8	1 - >8
	Gentamicin	30.0	--	70.0	>16	>16	≤0.12 - >16
	Levofloxacin	5.1	2.9	92.0	>8	>8	0.06 - >8
	Meropenem	0.0	24.6	75.4	32	>64	4 - >64
	Meropenem-vaborbactam	56.9	--	43.1	4	>16	≤0.06 - >16
	Piperacillin-tazobactam	0	--	100	>128	>128	32 - >128
Piperacillin-tazobactam-NS (1,271)	Cefepime-taniborbactam	98.2	--	1.8	0.25	2	0.015 - >16
	Cefepime	31.1	9.3	59.6	16	>16	≤0.25 - >16
	Ceftazidime	18.3	7.2	74.5	>16	>16	0.06 - >16
	Ceftazidime-avibactam	91.0	--	9.1	0.5	8	≤0.12 - >16
	Ceftolozane-tazobactam	41.5	--	58.5	8	>8	≤0.25 - >8
	Gentamicin	56.0	--	44.0	1	>16	≤0.12 - >16
	Levofloxacin	35.6	6.5	57.9	4	>8	0.015 - >8
	Meropenem	75.4	6.1	18.6	0.06	32	≤0.004 - >64
	Meropenem-vaborbactam	89.4	--	10.6	≤0.06	16	≤0.06 - >16
	Piperacillin-tazobactam	0	--	100	128	>128	16 - >128
ESBL-positive (156)[a]	Cefepime-taniborbactam	98.7	--	1.3	0.12	1	0.015 - >16
	Cefepime	5.8	11.5	82.7	>16	>16	0.5 - >16
	Ceftazidime	1.9	11.5	86.5	>16	>16	1 - >16
	Ceftazidime-avibactam	99.4	--	0.6	0.25	1	≤0.12 - >16
	Ceftolozane-tazobactam	75.6	--	24.4	1	>8	≤0.25 - >8
	Gentamicin	51.3	--	48.7	2	>16	0.25 - >16
	Levofloxacin	23.7	10.3	66.0	8	>8	0.03 - >8
	Meropenem	96.2	3.9	0.0	0.03	0.12	0.008 - 8
	Meropenem-vaborbactam	100	--	0	≤0.06	0.12	≤0.06 - 4
	Piperacillin-tazobactam	59.6	--	40.4	8	>128	≤4 - >128
KPC-positive (95)[b]	Cefepime-taniborbactam	100	--	0	1	2	0.03 - 8
	Cefepime	0	0	100	>16	>16	8 - >16
	Ceftazidime	0	0	100	>16	>16	8 - >16
	Ceftazidime-avibactam	96.8	--	3.2	2	4	≤0.12 - >16
	Ceftolozane-tazobactam	0	--	100	>8	>8	8 - >8
	Gentamicin	34.7	--	65.3	>16	>16	≤0.12 - >16
	Levofloxacin	4.2	1.1	94.7	>8	>8	0.06 - >8
	Meropenem	0.0	16.8	83.2	64	>64	4 - >64
	Meropenem-vaborbactam	97.9	--	2.1	0.25	2	≤0.06 - >16
	Piperacillin-tazobactam	0	--	100	>128	>128	64 - >128
MBL-positive (73)[c]	Cefepime-taniborbactam	84.9	--	15.1	1.0	16	0.03 - >16
	Cefepime	0.0	1.4	98.6	>16	>16	2 - >16
	Ceftazidime	0	0	100	>16	>16	16 - >16
	Ceftazidime-avibactam	1.4	--	98.6	>16	>16	4 - >16
	Ceftolozane-tazobactam	0	--	100	>8	>8	>8 - >8
	Gentamicin	20.6	--	79.5	>16	>16	0.25 - >16
	Levofloxacin	4.1	2.7	93.2	>8	>8	0.5 - >8
	Meropenem	2.7	11.0	86.3	32	>64	0.5 - >64
	Meropenem-vaborbactam	13.7	--	86.3	>16	>16	0.5 - >16
	Piperacillin-tazobactam	0	--	100	>128	>128	32 - >128
OXA-48-positive (76)[b]	Cefepime-taniborbactam	96.1	--	4.0	1	4	0.12 - >16
	Cefepime	10.5	2.6	86.8	>16	>16	≤0.25 - >16
	Ceftazidime	11.8	1.3	86.8	>16	>16	0.5 - >16
	Ceftazidime-avibactam	100	--	0	1	2	≤0.12 - 8
	Ceftolozane-tazobactam	5.3	--	94.7	>8	>8	≤0.25 - >8
	Gentamicin	31.6	--	68.4	>16	>16	≤0.12 - >16
	Levofloxacin	4.0	5.3	90.8	>8	>8	0.12 - >8
	Meropenem	13.2	35.5	51.3	16	64	0.25 - >64
	Meropenem-vaborbactam	48.7	--	51.3	16	>16	0.25 - >16
	Piperacillin-tazobactam	0	--	100	>128	>128	64 - >128

Cefepime-taniborbactam, cefepime with taniborbactam fixed at 4 mg/L; ceftazidime-avibactam, ceftazidime with avibactam fixed at 4 mg/L; ceftolozane-tazobactam, ceftolozane with tazobactam fixed at 4 mg/L; meropenem-vaborbactam, meropenem with vaborbactam fixed at 8 mg/L; TZP, piperacillin-tazobactam, piperacillin with tazobactam fixed at 4 mg/L; NS, nonsusceptible based on 2021 EUCAST breakpoints v11.0; breakpoint of ≤8 mg/L has been applied to cefepime-taniborbactam for comparative purposes.
[a]Note organisms could also possess AmpC-type enzymes, or OSBLs, but no carbapenemases
[b]Note organisms could also possess ESBLs, AmpC-type enzymes, or OSBLs, but no other carbapenemases
[c]Includes NDM (n=61) and VIM (n=12). Note organisms could also possess serine carbapenemases, ESBLs, AmpC-type enzymes, or OSBLs

Figure 3. MIC distribution of cefepime-taniborbactam and select comparator agents against 5,817 Enterobacterales

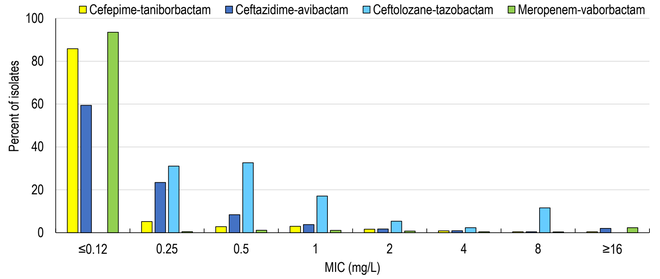
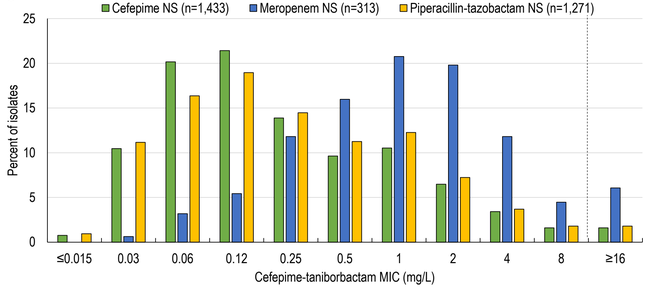
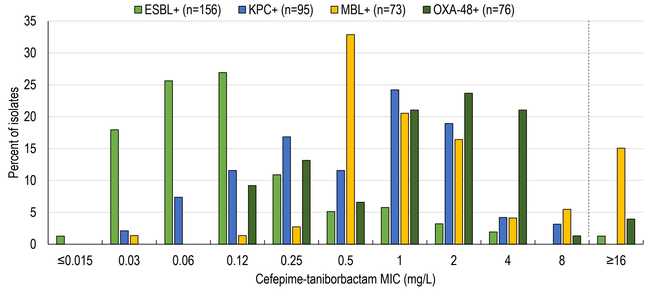


Figure 4. MIC distribution of cefepime-taniborbactam against resistant Enterobacterales



NS, non-susceptible based on 2021 EUCAST breakpoints; dashed line indicates the cefepime-taniborbactam provisional non-resistant breakpoint of ≤8 mg/L

Figure 5. MIC distribution of cefepime-taniborbactam against molecularly characterized Enterobacterales



Dashed line indicates the cefepime-taniborbactam provisional non-resistant breakpoint of ≤8 mg/L; MBLs consist of (n): NDM (61), VIM (12)

RESULTS SUMMARY

- Cefepime-taniborbactam showed potent *in vitro* activity against all Enterobacterales, with $MIC_{50/90}$ values of 0.06/0.25 mg/L and >99% inhibited at the provisional susceptible breakpoint of ≤8 mg/L (Table 1, Figure 3).
- Cefepime-taniborbactam activity was maintained against resistant subsets of Enterobacterales, with MIC_{90} values of 2 mg/L against cefepime-non-susceptible, 8 mg/L against meropenem-non-susceptible and 2 mg/L against piperacillin-tazobactam-non-susceptible isolates (Table 1, Figure 4).
- Cefepime-taniborbactam maintained activity against ESBL-, KPC-, OXA-48 group-, and MBL- (NDM=61, VIM=12) harboring isolates with MIC_{90} values of 1 mg/L, 2 mg/L, 4 mg/L, and 16 mg/L, respectively; 84.9% to 100% of MIC values of ≤8 mg/L) (Table 1, Figure 5).
- Whole genome sequence analysis suggested likely explanations for the majority of the isolates exhibiting cefepime-taniborbactam MIC values ≥16 mg/L, including penicillin-binding protein 3 variation observed in 4/6 (66.7%) *E. coli*, and permeability defects and/or possible efflux pump up-regulation in 12/12 (100%) *K. pneumoniae*.

CONCLUSIONS

Taniborbactam significantly restored the *in vitro* activity of cefepime against Enterobacterales, including isolates nonsusceptible to recently-approved BL/BLI combinations and expressing serine and metallo-β-lactamases. These findings support the continued development of cefepime-taniborbactam as a potential new treatment option for challenging infections due to resistant Gram negative pathogens.

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