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In vitro Activity of Ceftibuten in Combination with VNRX-5236 against Clinical Isolates of Enterobacterales from Urinary Tract Infections Collected in 2018-2020

IHMA, Inc.
2122 Palmer Drive
Schaumburg, IL 60173 USA
www.ihma.com

M. Hackel[1], M. Wise[1], D. Sahm[1]

[1]IHMA, Inc., Schaumburg, IL, USA

INTRODUCTION

Increasing resistance among agents commonly prescribed to treat urinary tract infections, including β-lactams, indicate that new oral agents are urgently needed. VNRX-7145 is being developed in combination with ceftibuten, an oral cephalosporin, to combat strains of Enterobacterales expressing extended spectrum β-lactamases (ESBLs) and serine carbapenemases [1, 2]. *In vivo*, VNRX-7145 (VNRX-5236 etzadroxil) is cleaved into the active inhibitor, VNRX-5236. VNRX-5236 is a reversible covalent inhibitor of serine β-lactamases, with a spectrum of inhibition that includes Ambler class A ESBLs, class C cephalosporinases, and class A and D carbapenemases (KPC and OXA-48, respectively). This study assessed the *in vitro* activity of ceftibuten/VNRX-5236 against 1,211 isolates of Enterobacterales from urinary tract infections (UTIs) from a 2018-2020 global culture collection.

METHODS

MICs of ceftibuten with VNRX-5236 fixed at 4 µg/mL and comparators were determined following CLSI M07-A11 guidelines [3] against 1,211 Enterobacterales collected globally (Figure 1, Figure 2). Quality control testing was performed each day of testing as specified by the CLSI [3, 4]. Isolates were from community and hospital urinary tract infections collected from 185 sites in 49 countries from 2018 to 2020. Clavulanate was tested at a 2:1 ratio in combination with amoxicillin, relebactam was tested at a fixed concentration of 4 µg/mL in combination with imipenem, and trimethoprim was tested in a 1:19 ratio with sulfamethoxazole. Resistant phenotypes were based on 2021 CLSI breakpoints [4]. As ceftibuten-VNRX-5236 breakpoints have not yet been established, the EUCAST ceftibuten susceptible breakpoint of ≤1 µg/mL was considered for comparative purposes [5]. The provisional breakpoint of ≤0.12 µg/mL was applied for tebipenem [6]. A set of 273 Enterobacterales with cefepime and/or ceftazidime MIC values of ≥2 mg/L was evaluated for the presence of acquired β-lactamase genes via PCR and Sanger sequencing.

RESULTS

Figure 1. Distribution of 1,211 Enterobacterales isolates by species

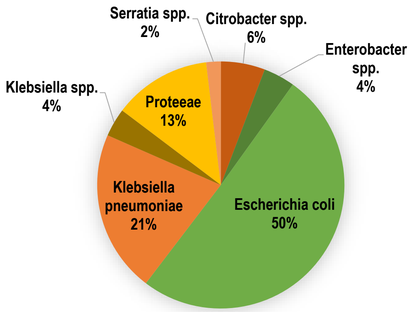


Figure 2. Distribution of 1,211 Enterobacterales isolates by region

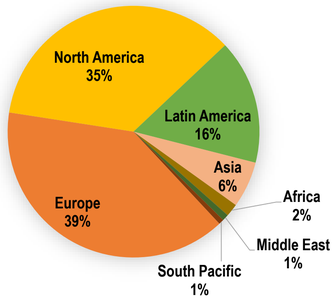
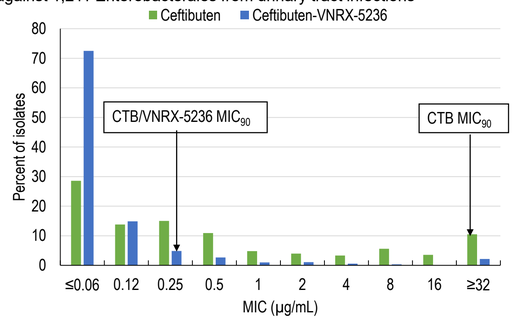


Table 1. *In vitro* activity of Ceftibuten-VNRX-5236 and comparator agents against 1,211 Enterobacterales from urinary tract infections

Phenotype (n)	Antimicrobial	%S	%I	%R	MIC_{50}	MIC_{90}	Range
All (1,211)	Ceftibuten/VNRX-5236	95.9	--	4.1	0.06	0.25	≤ 0.015 – > 32
	Ceftibuten	86.0	3.6	10.5	0.25	32	≤ 0.06 – > 32
	Amoxicillin/clavulanate	73.4	10.4	16.2	4	32	≤ 2 – > 32
	Cefazolin	41.3	9.7	49.1	4	> 32	≤ 0.5 – > 32
	Cefixime	66.3	3.7	30.0	0.5	> 8	≤ 0.06 – > 8
	Imipenem	89.2	5.7	5.1	0.12	2	≤ 0.03 – > 16
	Imipenem/relebactam	91.0	5.8	3.2	0.12	1	≤ 0.03 – > 8
	Levofloxacin	65.2	4.5	30.3	0.12	> 8	≤ 0.004 – > 8
	Nitrofurantoin	63.4	14.7	21.9	16	> 128	≤ 2 – > 128
	Sulopenem	na	na	na	0.03	0.5	0.015 – > 4
	Tebipenem	87.3	--	12.7	0.03	0.25	0.008 – > 4
	Trimethoprim/sulfa	64.7	--	35.3	≤ 0.25	> 4	≤ 0.25 – > 4
ESBL+ (165)[a]	Ceftibuten/VNRX-5236	97.0	na	3.0	0.12	0.25	0.03 – 32
	Ceftibuten	60.6	15.8	23.6	8	> 32	0.06 – 32
	Amoxicillin/clavulanate	73.3	23	3.6	8	16	2 – 32
	Cefazolin	0.6	0	99.4	> 32	> 32	1 – 32
	Cefixime	1.2	1.2	97.6	> 8	> 8	0.06 – 8
	Imipenem	98.2	1.2	0.6	0.12	0.25	0.06 – 4
	Imipenem/relebactam	98.2	1.8	0	0.12	0.25	0.06 – 2
	Levofloxacin	15.2	5.5	79.4	> 8	> 8	0.03 – 8
	Nitrofurantoin	76.4	7.3	16.4	16	> 128	2 – 64
	Sulopenem	na	na	na	0.03	0.12	0.03 – 1
	Tebipenem	94.5	na	5.5	0.03	0.12	0.015 – 2
	Trimethoprim/sulfa	29.7	0	70.3	> 4	> 4	0.25 – 4
Levofloxacin NS (421)	Ceftibuten/VNRX-5236	93.1	--	6.9	0.06	0.5	≤ 0.015 – > 32
	Ceftibuten	71.5	7.4	21.1	2	> 32	≤ 0.06 – > 32
	Amoxicillin/clavulanate	62.9	16.2	20.9	8	> 32	≤ 2 – > 32
	Cefazolin	16.9	8.6	74.6	> 32	> 32	≤ 0.5 – > 32
	Cefixime	38.2	3.6	58.2	> 8	> 8	≤ 0.06 – > 8
	Imipenem	82.7	7.4	10.0	0.12	2	0.06 – > 16
	Imipenem/relebactam	87.2	6.9	5.9	0.12	2	≤ 0.03 – > 8
	Levofloxacin	0	12.8	87.2	> 8	> 8	1 – > 8
	Nitrofurantoin	61.0	11.4	27.6	16	> 128	≤ 2 – > 128
	Sulopenem	na	na	na	0.06	1	0.015 – > 4
	Tebipenem	79.1	--	20.9	0.03	1	0.015 – > 4
	Trimethoprim/sulfa	36.1	--	63.9	> 4	> 4	≤ 0.25 – > 4
Trimethoprim-sulfa R (428)	Ceftibuten/VNRX-5236	93.2	--	6.8	0.06	0.5	≤ 0.015 – > 32
	Ceftibuten	76.6	6.5	16.8	1	> 32	≤ 0.06 – > 32
	Amoxicillin/clavulanate	68.0	13.6	18.5	8	32	≤ 2 – > 32
	Cefazolin	21.0	10	68.9	> 32	> 32	≤ 0.5 – > 32
	Cefixime	46.0	1.9	52.1	4	> 8	≤ 0.06 – > 8
	Imipenem	85.3	5.8	8.9	0.12	2	0.06 – > 16
	Imipenem/relebactam	89.3	5.6	5.1	0.12	2	≤ 0.03 – > 8
	Levofloxacin	37.1	8.4	54.4	2	> 8	0.03 – > 8
	Nitrofurantoin	65.0	12.1	22.9	16	> 128	≤ 2 – > 128
	Sulopenem	na	na	na	0.03	0.5	0.015 – > 4
	Tebipenem	82.2	--	17.8	0.03	0.5	0.015 – > 4
	Trimethoprim/sulfa	0	--	100	> 4	> 4	4 – > 4
Amoxicillin-clavulanate NS (322)	Ceftibuten/VNRX-5236	84.8	--	15.2	0.06	4	≤ 0.015 – > 32
	Ceftibuten	60.2	6.2	33.5	2	> 32	≤ 0.06 – > 32
	Amoxicillin/clavulanate	0	39.1	60.9	32	> 32	16 – > 32
	Cefazolin	0.9	1.6	97.5	> 32	> 32	1 – > 32
	Cefixime	32.0	9.3	58.7	> 8	> 8	≤ 0.06 – > 8
	Imipenem	72.3	11.2	16.5	0.5	8	0.06 – > 16
	Imipenem/relebactam	80.1	11.5	8.4	0.25	2	≤ 0.03 – > 8
	Levofloxacin	51.6	8.4	40.1	0.5	> 8	0.03 – > 8
	Nitrofurantoin	36.0	25.8	38.2	64	> 128	4 – > 128
	Sulopenem	na	na	na	0.12	> 4	0.03 – > 4
	Tebipenem	64.9	--	35.1	0.12	> 4	0.015 – > 4
	Trimethoprim/sulfa	57.5	--	42.5	0.5	> 4	≤ 0.25 – > 4
Serine carbapenemase + (21)[b]	Ceftibuten/VNRX-5236	100	--	0	0.12	> 32	≤ 0.015 – > 32
	Ceftibuten	42.3	7.7	50.0	16	> 32	0.12 – > 32
	Amoxicillin/clavulanate	0.0	0.0	100.0	> 32	> 32	32 – > 32
	Cefazolin	0.0	0	100.0	> 32	> 32	32 – > 32
	Cefixime	3.8	3.8	92.3	> 8	> 8	0.25 – > 8
	Imipenem	8.0	16.0	76.0	8	> 16	0.5 – > 16
	Imipenem/relebactam	57.7	19.2	23.1	0.5	> 8	0.12 – > 8
	Levofloxacin	19.2	11.5	69.2	> 8	> 8	0.03 – > 8
	Nitrofurantoin	15.4	15.4	69.2	> 128	> 128	16 – > 128
	Sulopenem	na	na	na	> 4	> 4	0.5 – > 4
	Tebipenem	0	--	100	> 4	> 4	0.5 – > 4
	Trimethoprim/sulfa	26.9	--	73.1	> 4	> 4	≤ 0.25 – > 4

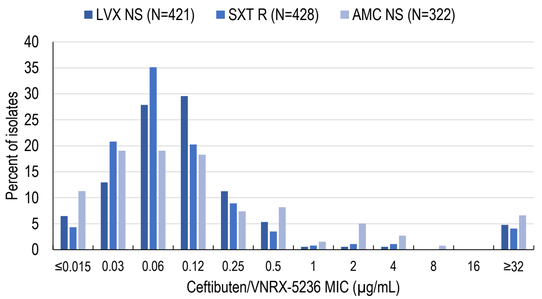
Ceftibuten/VNRX-5236, ceftibuten with VNRX-5236 fixed at 4 µg/mL; ESBL, extended spectrum β-lactamase positive; NS, nonsusceptible based on 2021 CLSI breakpoints; trimethoprim/sulfa, trimethoprim/sulfamethoxazole; breakpoint of ≤1 µg/mL has been applied to ceftibuten/VNRX-5236 for comparative purposes; a breakpoint of ≤0.12 µg/mL has been applied to tebipenem for comparative purposes.
[a]ESBL positive isolates may also contain AmpCs.
[b]Serine carbapenemases include 8 KPC-2, 4 KPC-3, 4 OXA-48, 1 OXA-181, 2 OXA-244, and 2 OXA-232. Isolates may also contain AmpCs and/or ESBLs.

Figure 3. MIC distribution of ceftibuten and ceftibuten/VNRX-5236 against 1,211 Enterobacterales from urinary tract infections



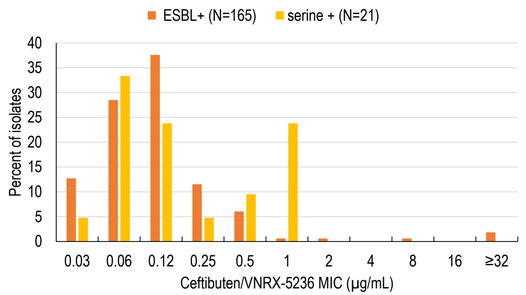
CTB, ceftibuten

Figure 4. MIC distribution of ceftibuten/VNRX-5236 against resistant Enterobacterales



LVX, levofloxacin; STX, trimethoprim -sulfamethoxazole; AMC, amoxicillin-clavulanate; NS, not susceptible; R, resistant

Figure 5. MIC distribution of ceftibuten/VNRX-5236 against ESBL-positive[a] and serine carbapenemase-positive[b] Enterobacterales



[a]ESBL positive isolates may also contain AmpCs.
[b]Serine carbapenemases include 8 KPC-2, 4 KPC-3, 4 OXA-48, 1 OXA-181, 2 OXA-244, and 2 OXA-232. Isolates may also contain AmpCs and/or ESBLs.

RESULTS SUMMARY

- The addition of VNRX-5236 reduced ceftibuten MIC_{90} values by ≥128-fold for all Enterobacterales isolates tested, with $MIC_{50/90}$ values of 0.06/0.25 µg/mL and 95.9% inhibited at ≤1 µg/mL (Table 1, Figure 3).
- A substantial percentage of isolates were non-susceptible to extended-spectrum β-lactams, levofloxacin, trimethoprim-sulfamethoxazole, and amoxicillin-clavulanate (Table 1).
- The rescue of ceftibuten by of the addition of VNRX-5236 was maintained against resistant subsets, including those not susceptible to levofloxacin (MIC_{90}, 0.5 µg/mL; 93.1% inhibited at ≤1 µg/mL), amoxicillin-clavulanate (MIC_{90}, 4 µg/mL; 84.8% inhibited at ≤2 µg/mL), and trimethoprim -sulfamethoxazole (MIC_{90}, 0.5 µg/mL; 93.2% inhibited at ≤1 µg/mL), (Table 1, Figure 4).
- Ceftibuten/VNRX-5236 maintained activity against ESBL+ isolates (n=165; MIC_{90}, 0.25 µg/mL; 97.0% inhibited at ≤1 µg/mL) (Table 1, Figure 5) and serine carbapenemase-positive isolates (n=21;100% inhibited at ≤1 µg/mL) (Table 1, Figure 5).

CONCLUSIONS

- Ceftibuten/VNRX-5236 exhibited promising *in vitro* activity against recent Enterobacterales from UTIs, and may have potential as an oral treatment option for complicated urinary tract infections, including those caused by serine β-lactamase-expressing Enterobacterales (ESBL, KPC, OXA-48/OXA-48-like) for which there are currently few oral treatment options available.

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