In Vitro Activity of WCK 4282 (High-Dose Cefepime-Tazobactam) Against Resistant Subsets of Enterobacteriaceae Collected Worldwide (2014)

P1261

HS SADER, PR RHOMBERG, M CASTANHEIRA, RN JONES
JMI Laboratories, North Liberty, IA, USA

ECCMID 2016
JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370, fax 319.665.3371
helio-sader@jmilabs.com

ABSTRACT

Background: WCK 4282 (cefepime-tazobactam) is being developed for treatment of serious Gram-negative infections at dosages of 2g/2g q8 and q12 hours. Cefepime-tazobactam was tested against clinical isolates of Enterobacteriaceae with extended-spectrum β-lactamase (ESBL) phenotype and those with chromosomal AmpC collected in medical centers worldwide as part of the SENTRY Antimicrobial Surveillance Program.

Methods: A total of 1,151 Enterobacteriaceae isolates with an ESBL-phenotype (*E. coli* [EC], *Klebsiella* spp. [KSP] and *P. mirabilis* [PM]), and 264 isolates from Enterobacteriaceae species with inducible cephalosporinases (AmpC-ENT; includes *Citrobacter* spp., *Enterobacter* spp., indole-positive Proteae and *Serratia* spp.) that exhibited decreased susceptibility to ceftazidime (ceftazidime-non-susceptible, CAZ-NS; MIC ≥8 mg/L) were tested for susceptibility by a reference broth microdilution method against cefepime-tazobactam (tazobactam at fixed 8 mg/L) and comparator agents.

Results: Overall ESBL rates were 21.3, 31.0 and 8.3% for EC, KSP and PM, respectively. ESBL-EC isolates were very susceptible to cefepime-tazobactam (98.7% inhibited at ≤8/8 mg/L [cefepime high-dose, CLSI]) and meropenem (99.4% susceptible), but showed decreased susceptibility to piperacillin-tazobactam (82.1%) and other agents (see Table). ESBL-PM isolates were very susceptible to cefepime-tazobactam, piperacillin-tazobactam and meropenem (100.0% susceptible); whereas ESBL-KSP showed higher resistance rates to most agents tested. Among ESBL-KSP, 73.7% of strains were inhibited at ≤8/8 mg/L of cefepime-tazobactam and 71.9% were susceptible to meropenem; whereas only 36.8% were susceptible to piperacillin-tazobactam. The most active β-lactams tested against CAZ-NS AmpC-Enterobacteriaceae were meropenem (96.6% susceptible) and cefepime-tazobactam (96.2% inhibited at ≤8/8 mg/L), and only 37.5% of isolates were susceptible to piperacillin-tazobactam. Among Enterobacteriaceae isolates non-susceptible to CAZ, ceftriaxone, gentamicin and levofloxacin (n=178), 96.1% were inhibited at ≤8/8 mg/L of cefepime-tazobactam and 97.2% were susceptible to meropenem.

Conclusions: WCK 4282 (cefepime-tazobactam) demonstrated potent *in vitro* activity against a large collection of antimicrobial-resistant Enterobacteriaceae strains, and exhibited a spectrum of activity comparable to meropenem and significantly superior to piperacillin-tazobactam and cefepime. These *in vitro* results support further clinical development of WCK 4282 (cefepime-tazobactam) for treatment of Gram-negative infections, including those caused by multidrug-resistant Enterobacteriaceae.

Antimicrobial	MIC_{50} / MIC_{90} /% susceptible [CLSI] (no. tested)			
	ESBL *E. coli* (471)	ESBL *Klebsiella* spp. (661)	ESBL *P. mirabilis* (19)	CAZ-NS AmpC-ENT[a] (264)
Cefepime-tazobactam	0.12/0.5/[96.2/98.7][b]	0.5/64/[65.5/73.7][b]	0.12/0.25/[100.0/100.0][b]	0.25/2/[92.8/96.2][b]
Cefepime	16/>64/23.4	32/>64/18.5	1/>64/57.9	0.5/16/74.6
Piperacillin-tazobactam	8/64/82.1	>64/>64/36.8	1/8/100.0	32/>64/37.5
Meropenem	≤0.06/≤0.06/99.4	≤0.06/>8/71.9	≤0.06/0.12/100.0	≤0.06/0.12/96.6
Levofloxacin	>4/>4/23.4	>4/>4/41.1	>4/>4/15.8	0.25/>4/77.7
Gentamicin	2/>8/51.8	>8/>8/46.3	4/>8/57.9	≤1/>8/79.2

a. Includes *Citrobacter* spp., *Enterobacter* spp., indole-positive Proteae and *Serratia* spp. with CAZ MIC ≥8 mg/L.
b. % inhibited at ≤2/≤8 mg/L (CLSI; cefepime low/high dose).

INTRODUCTION

WCK 4282 is a combination agent consisting of the fourth-generation oxyimino-cephalosporin cefepime and the β-lactamase inhibitor tazobactam. Cefepime was approved by the United States Food Drug Administration (US-FDA) in 1997, and has a broad-spectrum of activity against aerobic Gram-positive and Gram-negative bacteria, including *Pseudomonas aeruginosa*. The US-FDA clinical indications for cefepime include the treatment of moderate to severe pneumonia, complicated and uncomplicated urinary tract infections, complicated intraabdominal infections and uncomplicated skin and skin structure infections, as well as empiric therapy for febrile neutropenic patients. Cefepime doses are administered as a 30 min infusion.

The Clinical and Laboratory Standards Institute (CLSI) revised cefepime clinical breakpoints in 2014 after reviewing clinical and pharmacokinetic/pharmacodynamics (PK-PD) data as well as contemporary MIC distributions from large databases. According to the current CLSI breakpoint criteria for Enterobacteriaceae (M100-S26 document), the susceptible and resistant breakpoints are ≤2 and ≥16 mg/L, respectively; and Enterobacteriaceae isolates with cefepime MIC of 4 and 8 mg/L should be reported as "susceptible-dose dependent" (SDD). As stated in the M100-S26 document, this category (SDD) indicates that the "susceptible breakpoint" depends on the cefepime dosage used. The Enterobacteriaceae breakpoint of ≤2 mg/L should be applied for the 1g q12 hours dosage (low-dosage), whereas susceptible breakpoints of ≤4 mg/L should be applied for 1g q8 hours or 2g q12 hours dosages, and ≤8 mg/L for 2g q8 hours (high-dosage). Of note, for *Pseudomonas aeruginosa*, the cefepime breakpoint of ≤8 mg/L is based on 1g q8 hours or 2g q12 hours dosages.

Cefepime-tazobactam is currently under clinical development at 2g/2g q8 hours as well as q12 hours dosage as a 90 minute infusion. In this investigation, cefepime-tazobactam was tested against clinical isolates of Enterobacteriaceae exhibiting an extended-spectrum β-lactamase (ESBL) phenotype and those with inducible chromosomal AmpC showing decreased susceptibility (MIC, >4 mg/L) to ceftazidime.

MATERIALS AND METHODS

Organism collection: A total of 1,151 Enterobacteriaceae isolates with an ESBL-phenotype (*Escherichia coli*, *Klebsiella* spp. and *P. mirabilis*), and 264 isolates from Enterobacteriaceae species with inducible cephalosporinases (includes *Citrobacter* spp., *Enterobacter* spp., indole-positive Proteae and *Serratia* spp.) that exhibited decreased susceptibility to ceftazidime (ceftazidime-non-susceptible, CAZ-NS; MIC >4 mg/L) were evaluated. ESBL screen (+) phenotype was defined as a MIC at ≥2 mg/L for ceftriaxone or ceftazidime or aztreonam for the following organisms: *E. coli*, *K. pneumoniae*, *K. oxytoca* and *Proteus mirabilis* [CLSI, 2016]. The isolates were collected in 2013-2014 from medical centres located in Europe (615 isolates from 21 nations), North America (338 isolates from the United States), Latin America (187 isolates from four countries) and the Asia-Pacific region (100 isolates from China and 157 isolates from eight other countries) as part of the SENTRY Antimicrobial Surveillance Program coordinated by JMI Laboratories (North Liberty, Iowa USA).

Antimicrobial susceptibility testing: MIC values for cefepime-tazobactam and comparator agents were determined using CLSI broth microdilution method as described in CLSI document M07-A10 (2015). Cefepime was combined with tazobactam at fixed concentrations of 4 and 8 mg/L. Cefepime-susceptible breakpoints published in the CLSI document M100-S26 (2016) for low-dosage (≤2 mg/L; 1g q12 h) and high-dosage (≤8 mg/L; 2g q8 h) were applied for comparison purposes only. Susceptibility interpretations published by CLSI (document M100-S26; 2016) and EUCAST (http://www.eucast.org/clinical_breakpoints/; 2016) were applied for comparator agents, when available. Quality control (QC) was performed using *E. coli* ATCC 25922, ATCC 35218 and NCTC 13353, *Klebsiella pneumoniae* ATCC 700603 and ATCC BAA-1705, and *P. aeruginosa* ATCC 27853. All QC MIC results were within acceptable ranges as published in CLSI documents, including WCK 4282 (see poster # P0806).

RESULTS

- Overall ESBL rates were 21.3, 33.7, 17.1 and 8.3% for *E. coli*, *K. pneumoniae*, *K. oxytoca* and *P. mirabilis*, respectively, with great variations among the geographic regions (**Table 1**). Among *Enterobacter* spp. the percentages of isolates non-susceptible to ceftazidime varied from 22.2% in North America to 39.3-39.5% in Latin America and China (28.5% overall; **Table 1**).
- *E. coli* isolates with an ESBL-phenotype were very susceptible to cefepime-tazobactam ($MIC_{50/90}$, 0.12/0.5 mg/L and 98.7% inhibited at ≤8 mg/L when tested at fixed 8 mg/L of tazobactam; **Table 2**) and meropenem ($MIC_{50/90}$, ≤0.06/≤0.06 mg/L and 99.4% susceptible by CLSI and EUCAST criteria), but showed decreased susceptibility to piperacillin-tazobactam ($MIC_{50/90}$, 8/64 mg/L and 82.1/71.9% susceptible by CLSI/EUCAST) and other comparator agents (**Table 3**).
- Among ESBL-phenotype *Klebsiella* spp., 73.7% of strains were inhibited at ≤8/8 mg/L of cefepime-tazobactam ($MIC_{50/90}$, 0.5/64 mg/L at fixed 8 mg/L; **Table 2**) and susceptibility rates were (CLSI/EUCAST) 71.9/73.8% for meropenem ($MIC_{50/90}$, ≤0.06/>8 mg/L), 36.8/26.3% for piperacillin-tazobactam ($MIC_{50/90}$, >64/>64 mg/L), 46.3/43.0% for gentamicin ($MIC_{50/90}$, >8/>8 mg/L) and 83.7/73.2% for amikacin ($MIC_{50/90}$, 4/32 mg/L; **Table 3**).
- *P. mirabilis* isolates with an ESBL-phenotype (n=19) were very susceptible to cefepime-tazobactam ($MIC_{50/90}$, 0.12/0.25 mg/L, highest MIC, 0.5 mg/L; **Table 2**), piperacillin-tazobactam ($MIC_{50/90}$, 1/8 mg/L; 100.0% susceptible) and meropenem ($MIC_{50/90}$, ≤0.06/0.12 mg/L; 100.0% susceptible), but showed decreased susceptibility to levofloxacin ($MIC_{50/90}$, >4/>4 mg/L; 15.8/5.3% susceptible [CLSI/EUCAST]) and gentamicin ($MIC_{50/90}$, 4/>8 mg/L; 57.9/47.4% susceptible; data not shown).
- The most active β-lactams tested against ceftazidime-non-susceptible *Enterobacter* spp. (n=179) were meropenem ($MIC_{50/90}$, ≤0.06/0.25 mg/L; 94.4/96.1% susceptible [CLSI/EUCAST]) and cefepime-tazobactam ($MIC_{50/90}$, 0.25/2 mg/L; 96.1% inhibited at ≤8/8 mg/L), and only 28.5/15.6% of isolates were susceptible (CLSI/EUCAST) to piperacillin-tazobactam ($MIC_{50/90}$, 32/>64 mg/L; **Table 3**).
- Among Enterobacteriaceae species with inducible chromosomal AmpC and reduced susceptibility to ceftazidime (other than *Enterobacter* spp., n=85), cefepime-tazobactam inhibited 96.5% of isolates at ≤8/8 mg/L ($MIC_{50/90}$, 0.12/2 mg/L when tested with tazobactam at fixed 4 and 8 mg/L; **Table 2**).
- When tested against Enterobacteriaceae isolates non-susceptible to ceftazidime (MIC, ≥8 mg/L), ceftriaxone (MIC, ≥2 mg/L), gentamicin (MIC, ≥8 mg/L) and levofloxacin (MIC, ≥4 mg/L), 98.3% of strains (175/178) were inhibited at ≤8/8 mg/L of cefepime-tazobactam ($MIC_{50/90}$, 0.12/0.5 mg/L at fixed 8 mg/L; **Table 2**) and susceptibility rates were (CLSI/EUCAST) 97.2/97.2% for meropenem ($MIC_{50/90}$, ≤0.06/≤0.06 mg/L), 79.2/62.4% for piperacillin-tazobactam ($MIC_{50/90}$, 8/>64 mg/L) and 95.5/93.3% for amikacin ($MIC_{50/90}$, 4/16 mg/L; **Table 3**).

Table 1. Regional occurrence of resistance phenotypes.

Geographic region (no. tested)	% of isolates tested:					
	ESBL-phenotype[a]				CAZ-NS[b]	
	E. coli	KPN	*K. oxytoca*	*P. mirabilis*	ESP	MDR[c]
Europe (615)	19.3	49.3	22.6	14.9	28.9	11.9
North America (338)	14.4	16.2	12.9	1.1	22.2	13.1
Latin American (187)	37.4	58.0	18.8	13.3	39.3	14.4
APAC (157)[d]	18.8	29.3	22.7	0.0	33.8	10.7
China (118)	66.3	44.8	0.0	20.0	39.5	14.4
All (1,415)	21.3	33.7	17.1	8.3	28.5	12.6

Abbreviations: KPN = *K. pneumoniae*; ESP = *Enterobacter* spp.
a. ESBL phenotype defined as a MIC at ≥2 mg/L for ceftriaxone and/or ceftazidime and/or aztreonam (CLSI, 2016).
b. Ceftazidime-non-susceptible (MIC, ≥8 mg/L; CLSI, 2016).
c. Defined as non-susceptibility to ceftazidime (MIC, ≥8 mg/L), ceftriaxone (MIC, ≥2 mg/L), gentamicin (MIC, ≥8 mg/L) and levofloxacin (MIC, ≥4 mg/L).
d. Asia-Pacific region excluding China.

Table 3. Activity of cefepime-tazobactam combinations (fixed 4 and 8 mg/L of tazobactam) and comparator antimicrobial agents.

Antimicrobial agent/ Organism (no. tested)	MIC_{50}	MIC_{90}	CLSI[a]		EUCAST[a]	
			%S	%R	%S	%R
ESBL-phenotype *E. coli* (471)						
FEP-TAZ fixed 8 mg/L	0.12	0.5	(98.7)[b]	-	-	-
FEP-TAZ fixed 4 mg/L	0.12	1	(97.5)[b]	-	-	-
Cefepime	16	>64	23.4	55.2	16.3	69.2
Piperacillin-tazobactam	8	64	82.1	9.4	71.9	17.9
Ceftazidime	16	>16	33.1	51.4	11.0	66.9
Ceftriaxone	>8	>8	4.2	94.3	4.2	94.3
Meropenem	≤0.06	≤0.06	99.4	0.6	99.4	0.4
Levofloxacin	>4	>4	23.4	74.0	22.6	76.6
Gentamicin	2	>8	51.8	47.3	51.2	48.2
Amikacin	2	8	98.1	1.1	95.1	1.9
ESBL-phenotype *Klebsiella* spp (661)						
FEP-TAZ fixed 8 mg/L	0.5	64	(73.7)[b]	-	-	-
FEP-TAZ fixed 4 mg/L	1	>64	(68.2)[b]	-	-	-
Cefepime	32	>64	18.5	68.2	13.8	77.5
Piperacillin-tazobactam	>64	>64	36.8	51.1	26.3	63.2
Ceftazidime	>16	>16	17.2	72.2	8.9	82.8
Ceftriaxone	>8	>8	3.8	93.9	3.8	93.9
Meropenem	≤0.06	>8	71.9	26.2	73.8	20.0
Levofloxacin	>4	>4	41.1	54.8	38.5	58.9
Gentamicin	>8	>8	46.3	52.6	43.0	53.7
Amikacin	4	32	83.7	7.0	73.2	16.3
Ceftazidime-non-susceptible *Enterobacter* spp. (179)						
FEP-TAZ fixed 8 mg/L	0.25	2	(96.1)[b]	-	-	-
FEP-TAZ fixed 4 mg/L	0.5	4	(95.5)[b]	-	-	-
Cefepime	1	16	71.5	12.8	55.9	18.4
Piperacillin-tazobactam	32	>64	28.5	25.1	15.6	71.5
Ceftazidime	>16	>16	0.0	88.3	0.0	100.0
Ceftriaxone	>8	>8	0.0	100.0	0.0	100.0
Meropenem	≤0.06	0.25	94.4	3.9	96.1	1.1
Levofloxacin	≤0.12	>4	83.2	11.7	79.3	16.8
Gentamicin	≤1	>8	81.0	15.1	79.3	19.0
Amikacin	1	4	96.1	3.4	95.5	3.9
MDR (178)[c]						
FEP-TAZ fixed 8 mg/L	0.12	0.5	(98.3)[b]	-	-	-
FEP-TAZ fixed 4 mg/L	0.12	1	(96.6)[b]	-	-	-
Cefepime	32	>64	9.0	55.7	9.0	89.3
Piperacillin-tazobactam	8	>64	79.2	8.4	62.4	20.2
Meropenem	≤0.06	≤0.06	97.2	2.8	97.2	2.8
Amikacin	4	16	95.5	3.9	93.3	4.5

a. Criteria as published by CLSI (2016) and EUCAST (2016).
b. Percentage inhibited at ≤8 mg/L, according cefepime susceptible breakpoint for cefepime high dosage (2g q8 h) as published in the CLSI document M100-S26.
c. Isolates non-susceptible to ceftazidime (MIC, ≥8 mg/L), ceftriaxone (MIC, ≥2 mg/L), gentamicin (MIC, ≥8 mg/L) and levofloxacin (MIC, ≥4 mg/L). Includes *C. freundii* (one isolate), *E. aerogenes* (three isolates), *E. coli* (116 isolates), *K. pneumoniae* (51 isolates), *M. morganii* (two isolates), *P. mirabilis* (three isolates) and *Providencia stuartii* (three isolates).

Table 2. Cumulative frequency distributions of cefepime and WCK 4282 (cefepime + tazobactam [FEP-TAZ] at fixed concentrations of 4 and 8 mg/L) MIC results when tested against (1,415) bacterial isolates.

Resistance phenotype/ organism/antimicrobial agent	No. of organisms (cumulative percentage) inhibited at MIC (mg/L) of:													
	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64	MIC_{50}	MIC_{90}
ESBL-phenotype[a]														
E. coli (471)														
FEP-TAZ fixed 8 mg/L	235 (49.9)	112 (73.7)	65 (87.5)	22 (92.1)	5 (93.2)	14 (96.2)	6 (97.5)	6 (98.7)	3 (99.4)	1 (99.6)	0 (99.6)	2 (100.0)	0.12	0.5
FEP-TAZ fixed 4 mg/L	188 (39.9)	117 (64.8)	70 (79.6)	45 (89.2)	9 (91.1)	16 (94.5)	7 (96.0)	7 (97.5)	4 (98.3)	5 (99.4)	1 (99.6)	2 (100.0)	0.12	1
Cefepime	19 (4.0)	18 (7.9)	10 (10.0)	18 (13.8)	12 (16.3)	33 (23.4)	35 (30.8)	66 (44.8)	65 (58.6)	52 (69.6)	58 (82.0)	85 (100.0)	16	>64
Klebsiella spp. (661)														
FEP-TAZ fixed 8 mg/L	206 (31.2)	58 (39.9)	53 (48.0)	46 (54.9)	36 (60.4)	34 (65.5)	29 (69.9)	25 (73.7)	36 (79.1)	22 (82.5)	52 (90.3)	64 (100.0)	0.5	64
FEP-TAZ fixed 4 mg/L	160 (24.2)	72 (35.1)	46 (42.1)	46 (49.0)	36 (54.5)	35 (59.8)	28 (64.0)	28 (68.2)	49 (75.6)	18 (78.4)	52 (86.2)	91 (100.0)	1	>64
Cefepime	9 (1.4)	12 (3.2)	16 (5.6)	26 (9.5)	28 (13.8)	31 (18.5)	27 (22.5)	61 (31.8)	73 (42.8)	72 (53.7)	97 (68.4)	209 (100.0)	32	>64
P. mirabilis (19)														
FEP-TAZ fixed 8 mg/L	4 (21.1)	10 (73.7)	4 (94.7)	1 (100.0)									0.12	0.25
FEP-TAZ fixed 4 mg/L	5 (26.3)	7 (63.2)	6 (94.7)	1 (100.0)									0.12	0.25
Cefepime			2 (10.5)	1 (15.8)	7 (52.6)	1 (57.9)	1 (63.2)	3 (78.9)	0 (78.9)	0 (78.9)	1 (84.2)	3 (100.0)	1	>64
AmpC derepressed phenotype[b]														
Enterobacter spp.[c] (179)														
FEP-TAZ fixed 8 mg/L	12 (6.7)	41 (29.6)	45 (54.7)	32 (72.6)	23 (85.5)	12 (92.2)	4 (94.4)	3 (96.1)	3 (97.8)	2 (98.9)	1 (99.4)	1 (100.0)	0.25	2
FEP-TAZ fixed 4 mg/L	10 (5.6)	38 (26.8)	37 (47.5)	36 (67.6)	23 (80.4)	17 (89.9)	6 (93.3)	4 (95.5)	3 (97.2)	3 (98.9)	1 (99.4)	1 (100.0)	0.5	4
Cefepime	4 (2.2)	17 (11.7)	33 (30.2)	31 (47.5)	15 (55.9)	28 (71.5)	18 (81.6)	10 (87.2)	9 (92.2)	4 (94.4)	5 (97.2)	5 (100.0)	1	16
Other species[d] (85)														
FEP-TAZ fixed 8 mg/L	41 (48.2)	10 (60.0)	14 (76.5)	6 (83.5)	5 (89.4)	4 (94.1)	0 (94.1)	2 (96.5)	0 (96.5)	1 (97.6)	1 (98.8)	1 (100.0)	0.12	2
FEP-TAZ fixed 4 mg/L	32 (37.6)	12 (51.8)	9 (62.4)	16 (81.2)	7 (89.4)	2 (91.8)	2 (94.2)	1 (95.3)	1 (96.5)	0 (96.5)	2 (98.8)	1 (100.0)	0.12	2
Cefepime	17 (20.0)	20 (23.5)	11 (36.6)	17 (56.4)	14 (72.9)	7 (81.2)	4 (85.9)	4 (90.5)	0 (90.6)	2 (92.9)	4 (97.6)	2 (100.0)	0.5	8
MDR phenotype(178)[e]														
FEP-TAZ fixed 8 mg/L	79 (44.4)	48 (71.3)	25 (85.4)	11 (91.6)	1 (92.1)	5 (94.9)	4(97.2)	2 (98.3)	1 (98.9)	1 (99.4)	1 (100.0)		0.12	0.5
FEP-TAZ fixed 4 mg/L	45 (25.7)	63 (60.7)	33 (79.2)	16 (88.2)	4 (90.4)	4 (92.7)	3 (94.4)	3 (96.6)	4 (98.3)	2 (98.9)	1 (100.0)		0.12	1
Cefepime		2 (1.1)	4 (3.4)	7 (7.3)	3 (9.0)	0 (9.0)	3 (10.7)	22 (23.0)	38 (44.3)	34 (63.5)	35 (83.1)	30 (100.0)	32	>64

a. Defined as a MIC of ≥2 mg/L for ceftriaxone and/or ceftazidime and/or aztreonam (CLSI, 2016).
b. Defined as ceftazidime-non-susceptible (MIC, >4 mg/L; CLSI 2016).
c. Includes *Enterobacter aerogenes* (69 isolates) and *E. cloacae* (110 isolates).
d. Includes *Citrobacter freundii* (45 isolates) and *C. koseri* (two isolates), *Morganella morganii* (20 isolates), *Providencia stuartii* (14 isolates) and *Serratia marcescens* (four isolates)
e. Isolates non-susceptible to ceftazidime (MIC, ≥8 mg/L), ceftriaxone (MIC, ≥2 mg/L), gentamicin (MIC, ≥8 mg/L) and levofloxacin (MIC, ≥4 mg/L). Includes *C. freundii* (one isolate), *E. aerogenes* (three isolates), *E. coli* (116 isolates), *K. pneumoniae* (51 isolates), *M. morganii* (two isolates), *P. mirabilis* (three isolates) and *Providencia stuartii* (three isolates).

CONCLUSIONS

- WCK 4282 (cefepime-tazobactam) demonstrated potent *in vitro* activity against a large collection of antimicrobial-resistant Enterobacteriaceae strains, including MDR, ESBL and chromosomal AmpC derepressed phenotypes.
- WCK 4282 (cefepime-tazobactam) exhibited a spectrum of activity comparable to that of meropenem and significantly superior to piperacillin-tazobactam and cefepime.
- These *in vitro* results support further clinical development of WCK 4282 (cefepime-tazobactam) for treatment of Gram-negative infections, including those caused by MDR Enterobacteriaceae.

ACKNOWLEDGEMENTS

This study was supported by Wockhardt Limited.

REFERENCES

1. Burgess SV, Mabasa VH, Chow I, Ensom MH (2015). Evaluating outcomes of alternative dosing strategies for cefepime: a qualitative systematic review. *Ann Pharmacother* 49: 311-322.
2. Clinical and Laboratory Standards Institute (2016). *M100-S26. Performance standards for antimicrobial susceptibility testing: 26th informational supplement*. Wayne, PA: CLSI.
3. EUCAST (2016). Breakpoint tables for interpretation of MICs and zone diameters. Version 6.0, January 2016. Available at: http://www.eucast.org/clinical_breakpoints/. Accessed January 2016.
4. Maxipime Package Insert (2012). Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050679s036lbl.pdf. Accessed February 18, 2016.
5. Nguyen HM, Shier KL, Graber CJ (2014). Determining a clinical framework for use of cefepime and beta-lactam/beta-lactamase inhibitors in the treatment of infections caused by extended-spectrum-beta-lactamase-producing Enterobacteriaceae. *J Antimicrob Chemother* 69: 871-880.