

CEFTAZIDIME-AVIBACTAM ACTIVITY TESTED AGAINST SELECT GRAM-NEGATIVE ORGANISMS FROM A GLOBAL SURVEILLANCE PROGRAM (2011) IN RELATION TO THE CEFTAZIDIME EPIDEMIOLOGIC CUT-OFF VALUE

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Objectives: The effect of avibactam (AVI) on the activity of ceftazidime (CAZ) as measured by the CAZ-AVI MIC frequency distribution of select Gram-negative (GN) clinical isolates from the SENTRY Antimicrobial Surveillance Program was compared to European Committee for Antimicrobial Susceptibility Testing (EUCAST) MIC epidemiological cut-off values (ECOFFs) listed for CAZ. CAZ-AVI, a combination of CAZ and the novel non- β -lactam β -lactamase inhibitor AVI, targets GN bacteria and is currently in clinical development.

Methods: The activity of CAZ-AVI and CAZ as measured in the 2011 SENTRY Antimicrobial Surveillance Program for select GN bacteria for each region (Europe and Mediterranean, USA, Asia-Pacific, and Latin American region) was compared to ECOFF values from the EUCAST website (accessed at <http://mic.eucast.org> [14 November 2013]; See Table). Clinically relevant isolates were collected at medical centers from a variety of infection sites, including bloodstream, respiratory, skin and soft tissue, urinary and others. Susceptibility testing for CAZ and CAZ-AVI was conducted according to Clinical and Laboratory Standards Institute guidelines using validated dry-form broth microdilution panels. AVI was tested at a fixed concentration of 4 mg/L.

Results: For *Escherichia coli*, CAZ-AVI MIC₅₀/MIC₉₀ values ranged from 0.06-0.12/0.12-0.25 mg/L, respectively across all regions (EUCAST CAZ ECOFF, 0.5 mg/L). The CAZ MIC₉₀ values for *E. coli* varied regionally from 2->32 mg/L. For *Klebsiella pneumoniae*, CAZ-AVI MIC₅₀ values were 0.12 mg/L in each region and MIC₉₀ values ranged from 0.25-0.5 mg/L (EUCAST CAZ ECOFF, 0.5 mg/L). The MIC₉₀ values for CAZ for *K. pneumoniae* were >32 mg/L in each region. The MIC₉₀ for CAZ-AVI for *Enterobacter cloacae* ranged from 0.5-1 mg/L (EUCAST CAZ ECOFF, 1 mg/L). The MIC₉₀ for CAZ in each region was >32 mg/L. The MIC₉₀ for CAZ-AVI for *Citrobacter* spp. ranged from 0.25-0.5 mg/L (CAZ ECOFF, 1 mg/L). The MIC₉₀ for CAZ in each region was >32 mg/L. *Morganella morganii* and *Proteus mirabilis* MIC₉₀ values ranged from 0.06-0.25 mg/L and 0.06-0.12 mg/L, respectively for CAZ-AVI (CAZ ECOFF values, 0.25 and 0.12 mg/L, respectively). MIC₉₀ values for CAZ-AVI against *Serratia marcescens* were 0.5 mg/L for all regions (EUCAST CAZ ECOFF, 0.5 mg/L). *Haemophilus influenzae* MIC₉₀ values ranged from \leq 0.03-0.06 mg/L (EUCAST CAZ ECOFF, 0.5 mg/L). *Pseudomonas aeruginosa* MIC₉₀ values for CAZ-AVI ranged from 8-16 mg/L while CAZ MIC₉₀ values ranged from 32->32 mg/L (EUCAST CAZ ECOFF, 8 mg/L). A total of 86.2-95.8% of *P. aeruginosa* isolates per region exhibited CAZ-AVI MIC values \leq 8mg/L (66.2-83.1% for CAZ only).

Conclusions: CAZ-AVI was highly active against select GN isolates from European, USA, Asia-Pacific, and Latin American regions. CAZ-AVI MIC₉₀ values for most GN isolates were lowered to the ECOFF MIC value for CAZ alone or lower, demonstrating the beneficial effect of the addition of AVI.

Table.

Organism (N)	Ceftazidime-avibactam MIC in mg/L by region: ^a								EUCAST ECOFF (CAZ) in mg/L
	EMR		USA		LATAM		APAC		
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	
<i>Enterobacteriaceae</i>	(N=4627) 0.06	0.25	(N=3233) 0.12	0.25	(N=1444) 0.12	0.25	(N=1958) 0.12	0.25	
<i>Escherichia coli</i>	(N=2113) 0.06	0.12	(N=718) 0.06	0.12	(N=517) 0.06	0.25	(N=670) 0.12	0.25	0.5
<i>Klebsiella pneumoniae</i>	(N=858) 0.12	0.5	(N=818) 0.12	0.25	(N=373) 0.12	0.5	(N=445) 0.12	0.25	0.5
<i>Enterobacter cloacae</i>	(N=428) 0.12	0.5	(N=379) 0.12	0.5	(N=172) 0.25	1	(N=219) 0.25	1	1
<i>Citrobacter</i> spp	(N=200) 0.12	0.25	(N=272) 0.12	0.25	(N=51) 0.12	0.5	(N=146) 0.12	0.5	1
<i>Morganella morganii</i>	(N=165) \leq 0.03	0.12	(N=192) 0.06	0.12	(N=61) 0.06	0.25	(N=133) \leq 0.03	0.06	0.25
<i>Proteus mirabilis</i>	(N=270) \leq 0.03	0.06	(N=230) \leq 0.03	0.06	(N=57) \leq 0.03	0.12	(N=56) \leq 0.03	0.06	0.12
<i>Serratia marcescens</i>	(N=273) 0.12	0.5	(N=237) 0.12	0.5	(N=118) 0.12	0.5	(N=161) 0.12	0.5	0.5
<i>Pseudomonas aeruginosa</i>	(N=1137) 2	16	(N=213) 2	8	(N=517) 2	16	(N=612) 2	8	8
<i>Haemophilus influenzae</i>	(N=758) \leq 0.03	\leq 0.03	(N=909) \leq 0.03	\leq 0.03	(N=126) \leq 0.03	\leq 0.03	(N=323) \leq 0.03	0.06	0.5

a. Abbreviations: EMR, European and Mediterranean; LATAM, Latin America; APAC, Asia-Pacific