

In-vitro Activity of Ceftobiprole Against Select Gram-positive and Gram-negative Pathogens Isolated From Europe in 2006-2007

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Abstract

Objective: Ceftobiprole (BPR) is a pyrrolidone-3-ylidene-methyl cephalosporin with activity against a broad spectrum of clinically relevant pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA). BPR is intended for use in hospitals against infections where resistant Gram-positive (GP) and Gram-negative (GN) bacteria, particularly MRSA, are suspected. As such, BPR is currently being developed to treat hospital-acquired pneumonia (HAP) and complicated skin and skin-structure infections (cSSSI). The current surveillance initiative assessed the *in-vitro* activity of BPR and comparator agents against GP and GN European (EU) clinical isolates from the past year.

Methods: During 2006 and 2007, GP (*S. aureus* [SA], coagulase-negative staphylococci [CoNS], and *Streptococcus pneumoniae* [SP]) and GN (Enterobacteriaceae [EN] and *Pseudomonas aeruginosa* [PA]) clinical isolates were collected from 28 laboratories in 11 EU countries. All isolates were centrally tested by broth microdilution (CLSI; M7-A7) at Eurofins Medinet, Inc.

Results:

Organism	Phenotype	Total n	BPR MIC (mg/L)			
			Range	Mode	MIC ₅₀	MIC ₉₀
SA	All	1010	≤0.12-4	1	0.5	2
	MSSA	272	≤0.12-2	0.25	0.25	0.5
	MRSA	738	≤0.12-4	1	1	2
CoNS	All	378	≤0.12-4	1	0.5	2
	MS CoNS	114	≤0.12-1	≤0.12	≤0.12	0.25
	MR CoNS	264	≤0.12-4	1	1	2
SP	All	432	≤0.002-0.5	0.008	0.008	0.25
	PEN S	335	≤0.002-0.06	0.008	0.008	0.015
	PEN NS	97	0.004-0.5	0.25	0.25	0.5
EN	All	1912	≤0.015-32	0.03	0.03	16
	CAZ S	1656	≤0.015-32	0.03	0.03	16
	CAZ NS	256	0.03-32	32	32	>32
PA	All	533	0.06-32	2	4	16
	CAZ S	421	0.06-32	2	2	8
	CAZ NS	112	2-32	32	16	>32

Against the tested SA, the MIC₉₀s of BPR (2 mg/L) were similar to those of vancomycin (1 mg/L) and linezolid (2 mg/L). BPR MICs against MRSA were ≤2 mg/L with the exception of 1.3% of MRSA isolates which had BPR MICs of 4 mg/L. Against EN and PA, BPR was similar to cefepime (FEP) by both MIC₅₀/MIC₉₀ (FEP: 0.06/4 mg/L for EN and 4/16 mg/L for PA).

Conclusion: Ceftobiprole had potent *in-vitro* activity against the tested GP pathogens, regardless of resistance to methicillin or PEN. Ceftobiprole was comparable to cefepime against both ceftazidime-S and ceftazidime-NS EN and PA, though MICs of both cefepime and ceftobiprole were elevated against the ceftazidime-NS isolates. These results show the potential of ceftobiprole for the treatment of HAP and cSSSIs. As ceftobiprole is intended for use in hospitals where resistance is common, continued surveillance of ceftobiprole activity against target pathogens is warranted.

Objective

Gram-positive cocci and Gram-negative bacilli are commonly encountered pathogens in hospitals that can be difficult to treat due to antibiotic resistance. Ceftobiprole is an investigational pyrrolidone-3-ylidene-methyl cephalosporin with activity against a broad spectrum of both Gram-negative and Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA). Ceftobiprole has completed clinical trials for the treatment of hospital-acquired pneumonia and complicated skin and skin-structure infections (cSSSI), and is currently awaiting regulatory approval in the United States. In support of its clinical development in Europe, this surveillance initiative assessed the *in-vitro* activity of ceftobiprole and comparator agents against targeted Gram-positive and Gram-negative pathogens of European origin from 2006 to 2007.

Methods

Gram-positive and Gram-negative clinical isolates were collected from 28 hospital laboratories in 11 European countries (France, Italy, Spain, the United Kingdom, Germany, Belgium, Czech Republic, Hungary, the Netherlands, Poland, and Sweden) from 2006 to 2007. Gram-positive organisms consisted of 1010 *S. aureus*, 378 coagulase-negative *S. aureus* (CoNS), and 432 *Streptococcus pneumoniae*. Gram-negative organisms consisted of 1912 Enterobacteriaceae (547 *Escherichia coli*, 412 *Klebsiella pneumoniae*, 254 *Proteus mirabilis*, 213 *Citrobacter* spp., 246 *Enterobacter cloacae*, and 240 *Serratia marcescens*) and 533 *Pseudomonas aeruginosa*. All isolates were centrally tested by broth microdilution at Eurofins Medinet, Inc. (Herndon, VA, USA) according to CLSI M7-A7 guidelines. Ceftobiprole activity was analyzed along with other relevant comparator agents according to resistant phenotypes. CLSI M100-S17 breakpoints were used to interpret all comparator agents, where applicable.

Results

Gram-positive

S. aureus

Overall, ceftobiprole was active against *S. aureus* with an MIC range of ≤0.12-4 mg/L, and MIC₅₀ of 0.5 mg/L and an MIC₉₀ of 2 mg/L. Against methicillin-susceptible *S. aureus* (MSSA), ceftobiprole had an MIC₅₀ of 0.25 mg/L and an MIC₉₀ of 0.5 mg/L; and against MRSA the ceftobiprole MIC₅₀ was 1 mg/L and the MIC₉₀ was 2 mg/L (Table 1).

Ceftobiprole MIC₅₀s were similar to those of currently utilized Gram-positive agents (linezolid [2 mg/L], daptomycin [0.5 mg/L], and vancomycin [1 mg/L]) (Table 1). Against one daptomycin non-susceptible isolate, ceftobiprole had an MIC of 0.5 mg/L.

Based on MIC distributions, MSSA MICs were approximately two to four doubling dilutions lower than MRSA (Figure 1a). Ceftobiprole MICs against MRSA did not exceed 4 mg/L, which was observed for 1.2% of all *S. aureus* isolates.

CoNS

Against CoNS overall, ceftobiprole had an MIC₅₀ of 0.5 mg/L and an MIC₉₀ of 2 mg/L. Ceftobiprole showed an MIC₅₀ of ≤0.12 mg/L and an MIC₉₀ of 0.25 mg/L against methicillin-susceptible CoNS; and an MIC₅₀ of 1 mg/L and an MIC₉₀ of 2 mg/L against methicillin-resistant CoNS (Table 1). 4.0% of all CoNS isolates had MICs of 4 mg/L.

Ceftobiprole MIC₅₀s against CoNS were also similar to those of currently utilized Gram-positive agents (linezolid [1 mg/L], daptomycin [0.5 mg/L], and vancomycin [2 mg/L]) (Table 1).

Based on MIC distributions, ceftobiprole MICs against methicillin-resistant CoNS were elevated (4-8-fold) relative to methicillin-susceptible CoNS (Figure 1b).

S. pneumoniae

Based on MIC₅₀ and MIC₉₀ overall, ceftobiprole activity was greater than comparator agents ceftriaxone, cefuroxime, and linezolid.

Against penicillin susceptible *S. pneumoniae*, ceftobiprole had an MIC₅₀ of 0.015 mg/L; and an MIC₉₀ of 0.5 mg/L was observed for ceftobiprole against penicillin non-susceptible *S. pneumoniae* (Table 1).

By MIC distribution (Figure 1c), activity of ceftobiprole against penicillin-susceptible *S. pneumoniae* was lower than activity against penicillin non-susceptible *S. pneumoniae*. Regardless of phenotype, ceftobiprole MICs did not exceed 0.5 mg/L.

Figure 1a-c. MIC (mg/L) distribution of ceftobiprole against Gram-positive organisms according to phenotype

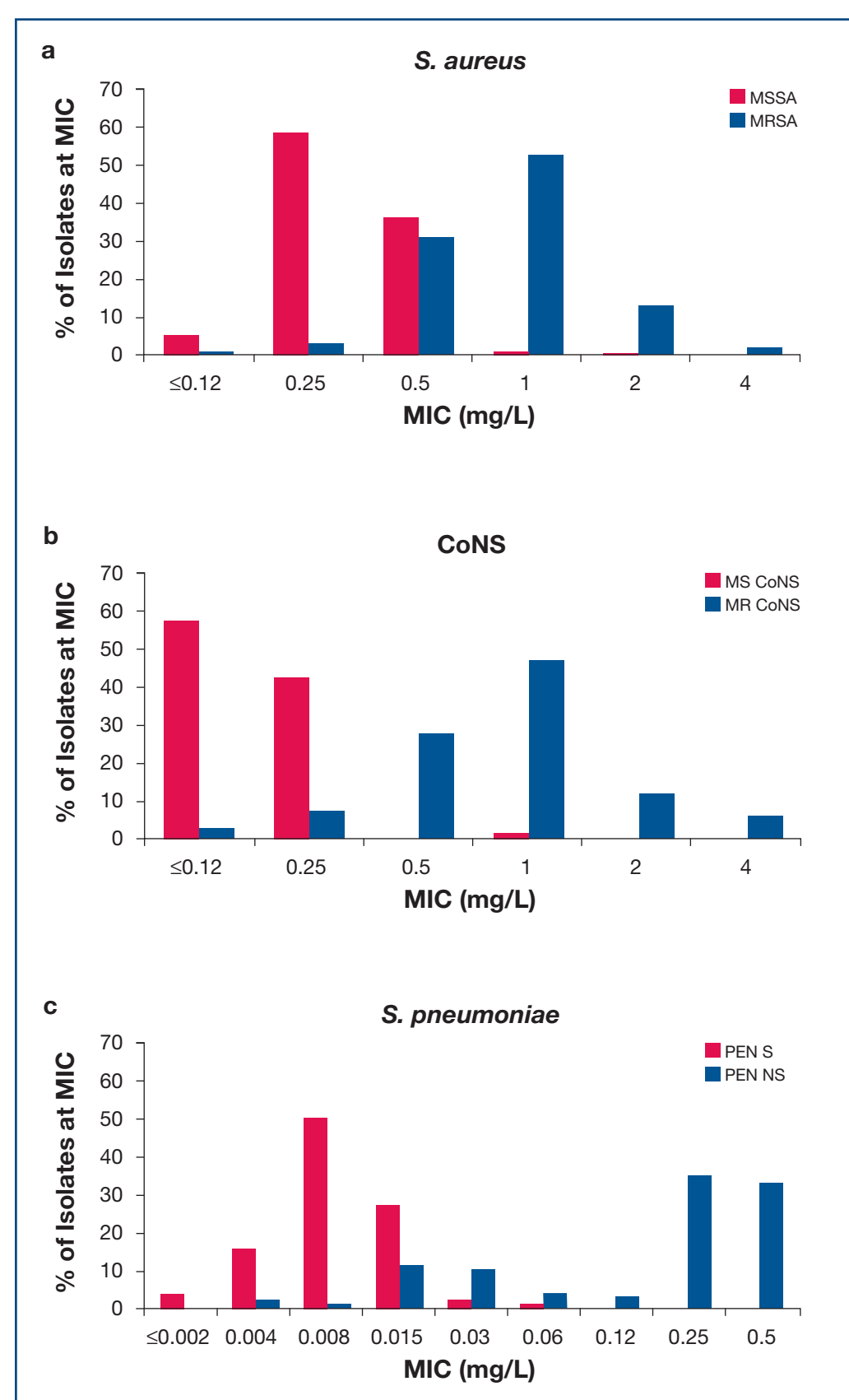


Table 1. MIC (mg/L) activity of ceftobiprole and comparators against Gram-positive organisms

Organism	Agent	Phenotype ^a	Total n	MIC (mg/L)				nS (%S)	nI (%I)	nR (%R)
				Range	Mode	MIC ₅₀	MIC ₉₀			
<i>S. aureus</i>	Ceftobiprole	All	1010	≤0.12-4	1	0.5	2	- ^b	-	-
		MSSA	272	≤0.12-2	0.25	0.25	0.5	-	-	-
		MRSA	738	≤0.12-4	1	1	2	-	-	-
	Linezolid	All	1010	≤0.25-4	1	1	2	1010 (100)	-	-
		MSSA	272	0.5-4	1	1	2	272 (100)	-	-
		MRSA	738	≤0.25-4	1	1	2	738 (100)	-	-
	Clindamycin	All	1010	≤0.03-32	0.12	0.12	>4	704 (69.7)	3 (0.3)	303 (30.0)
		MSSA	272	0.06-32	0.12	0.12	>4	266 (97.8)	0 (0)	6 (2.2)
		MRSA	738	≤0.03-32	0.12	0.12	>4	438 (59.3)	3 (0.4)	297 (40.2)
	Daptomycin	All	1010	≤0.12-2	0.25	0.25	0.5	1009 (99.9)	-	-
		MSSA	272	≤0.12-1	0.25	0.25	0.5	272 (100)	-	-
		MRSA	738	≤0.12-2	0.25	0.25	0.5	737 (99.9)	-	-
Erythromycin	All	1010	≤0.12-8	>8	>8	>8	474 (46.9)	3 (0.3)	533 (52.8)	
	MSSA	272	≤0.12-8	0.5	0.5	>8	230 (84.6)	1 (0.4)	41 (15.1)	
	MRSA	738	≤0.12-8	>8	>8	>8	244 (33.1)	2 (0.3)	492 (66.7)	
Vancomycin	All	1010	≤0.25-2	1	1	1	1010 (100)	0 (0)	0 (0)	
	MSSA	272	0.5-2	1	1	1	272 (100)	0 (0)	0 (0)	
	MRSA	738	≤0.25-2	1	1	1	738 (100)	0 (0)	0 (0)	
CoNS ^c	Ceftobiprole	All	378	≤0.12-4	1	0.5	2	-	-	-
		MS CoNS	114	≤0.12-1	≤0.12	≤0.12	0.25	-	-	-
		MR CoNS	264	≤0.12-4	1	1	2	-	-	-
	Linezolid	All	378	0.5-2	1	1	1	378 (100)	-	-
		MS CoNS	114	0.5-2	1	1	1	114 (100)	-	-
		MR CoNS	264	0.5-2	1	1	1	264 (100)	-	-
	Clindamycin	All	378	≤0.03-32	0.06	0.12	>4	296 (78.3)	3 (0.8)	79 (20.9)
		MS CoNS	114	≤0.03-32	0.06	0.06	0.12	109 (95.6)	1 (0.9)	4 (3.5)
		MR CoNS	264	≤0.03-32	0.06	0.12	>4	187 (70.8)	2 (0.8)	75 (28.4)
	Daptomycin	All	378	≤0.12-2	0.5	0.5	0.5	377 (99.7)	-	-
		MS CoNS	114	≤0.12-1	0.5	0.5	0.5	114 (100)	-	-
		MR CoNS	264	≤0.12-2	0.5	0.5	0.5	263 (99.6)	-	-
Erythromycin	All	378	≤0.12-8	>8	>8	>8	175 (46.3)	3 (0.8)	200 (52.9)	
	MS CoNS	114	≤0.12-8	0.25	0.25	>8	82 (71.9)	2 (1.8)	30 (26.3)	
	MR CoNS	264	≤0.12-8	>8	>8	>8	93 (35.2)	1 (0.4)	170 (64.4)	
Vancomycin	All	378	0.5-2	2	1	2	378 (100)	0 (0)	0 (0)	
	MS CoNS	114	0.5-2	1	1	2	114 (100)	0 (0)	0 (0)	
	MR CoNS	264	0.5-2	2	2	2	264 (100)	0 (0)	0 (0)	
<i>S. pneumoniae</i>	Ceftobiprole	All	432	≤0.002-0.5	0.008	0.008	0.25	-	-	-
		PEN S	335	≤0.002-0.06	0.008	0.008	0.015	-	-	-
		PEN NS	97	0.004-0.5	0.25	0.25	0.5	-	-	-
	Ceftriaxone ^d	All	432	≤0.015-8	≤0.015	≤0.015	0.5	427 (98.8)	4 (0.9)	1 (0.2)
		PEN S	335	≤0.015-0.5	≤0.015	≤0.015	0.03	335 (100)	0 (0)	0 (0)
		PEN NS	97	≤0.015-8	1	0.5	1	92 (94.8)	4 (4.1)	1 (1.0)
	Cefuroxime	All	432	≤0.015-8	0.03	0.03	4	361 (83.6)	5 (1.2)	66 (15.3)
		PEN S	335	≤0.015-4	0.03	0.03	0.12	333 (99.4)	1 (0.3)	1 (0.3)
		PEN NS	97	0.03-8	4	4	8	28 (28.9)	4 (4.1)	65 (67.0)
	Linezolid	All	432	≤0.25-1	1	1	1	432 (100)	-	-
		PEN S	335	≤0.25-1	1	1	1	335 (100)	-	-
		PEN NS	97	0.5-1	1	1	1	97 (100)	-	-
Clindamycin	All	432	≤0.015-32	0.06	0.06	>2	338 (78.2)	2 (0.5)	92 (21.3)	
	PEN S	335	≤0.015-2	0.06	0.06	>2	296 (88.4)	1 (0.3)	38 (11.3)	
	PEN NS	97	0.03-32	>2	>2	>2	42 (43.3)	1 (1.0)	54 (55.7)	
Erythromycin	All	432	≤0.015-32	0.03	0.06	>1	293 (67.8)	1 (0.2)	138 (31.9)	
	PEN S	335	≤0.015-1	0.03	0.03	>1	267 (79.7)	1 (0.3)	67 (20.0)	
	PEN NS	97	≤0.015-32	>1	>1	>1	26 (26.6)	0 (0)	71 (73.2)	

^aMSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; PEN, penicillin; S, susceptible; NS, non-susceptible
^bDashed lines indicate that CLSI interpretive breakpoints for susceptible (S), intermediate (I), and/or resistant (R) are not available
^cCoagulase-negative staphylococci
^dCLSI ceftriaxone nonmerging/intermediate breakpoints were applied

Table 2. MIC (mg/L) activity of ceftobiprole and comparator agents against Gram-negative organisms

Organism	Agent	Phenotype ^a	Total n	MIC (mg/L)				nS (%S)	nI (%I)	nR (%R)
				Range	Mode	MIC ₅₀	MIC ₉₀			
Enterobacteriaceae	Ceftobiprole	All	1912	≤0.015-32	0.03	0.03	16	- ^b	-	-
		CAZ S	1656	≤0.015-32	0.03	0.03	0.12	-	-	-
		CAZ NS	256	0.03-32	>32	>32	>32	-	-	-
	Ceftazidime	All	1912	≤0.03-32	0.12	0.12	32	1656 (86.6)	31 (1.6)	225 (11.8)
		CAZ S	1656	≤0.03-8	0.12	0.12	0.5	1656 (100)	0 (0)	0 (0)
		CAZ NS	256	0.12-32	>32	>32	>32	0 (0)	31 (12.1)	225 (87.9)
	Cefepime	All	1912	≤0.015-32	0.03	0.06	4	1782 (93.2)	18 (0.9)	112 (5.9)
		CAZ S	1656	≤0.015-32	0.03	0.03	0.12	1631 (98.5)	0 (0)	25 (1.5)
		CAZ NS	256	0.03-32	8	>32	8	151 (59.0)	18 (7.0)	87 (34.0)
	Ceftriaxone	All	1912	≤0.015-64	0.06	0.06	>64	1606 (84.0)	54 (2.8)	252 (13.2)
		CAZ S	1656	≤0.015-64	0.06	0.06	0.5	1588 (95.9)	19 (1.1)	49 (3.0)
		CAZ NS	256	0.5-64	>64	>64	>64	18 (7.0)	35 (13.7)	203 (79.3)
<i>P. aeruginosa</i>	Ceftobiprole	All	533	0.06-32	2	4	16	-	-	-
		CAZ S	421	0.06-32	2	2	8	-	-	-
		CAZ NS	112	2-32	>32	16	>32	-	-	-
	Ceftazidime	All	533	0.25-32	2	2	32	421 (79.0)	31 (5.8)	81 (15.2)
		CAZ S	421	0.25-8	2	2	8	421 (100)	0 (0)	0 (0)
		CAZ NS	112	16-32	>32	32	>32	0 (0)	31 (2	