

Rationale for EUCAST clinical breakpoints

Agent	Ceftolozane/tazobactam	
Current version	1.0	15 May 2020
Previous versions		

Foreword

EUCAST

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) is organised by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), the European Centre for Disease Prevention and Control (ECDC), and the active national antimicrobial breakpoint committees in Europe. EUCAST was established by ESCMID in 1997, was restructured in 2001-2002 and has been in operation in its current form since 2002. The current remit of EUCAST is to harmonise clinical breakpoints for existing drugs in Europe, to determine clinical breakpoints for new drugs, to set epidemiological (microbiological) breakpoints, to revise breakpoints as required, to harmonise methodology for antimicrobial susceptibility testing, to develop a website with MIC and zone diameter distributions of antimicrobial agents for a wide range of organisms and to liaise with European governmental agencies and European networks involved with antimicrobial resistance and resistance surveillance.

Information on EUCAST and EUCAST breakpoints is available on the EUCAST website at <http://www.eucast.org>.

EUCAST rationale documents

EUCAST rationale documents summarise the information on which the EUCAST clinical breakpoints are based.

Availability of EUCAST documents

All EUCAST documents are freely available from the EUCAST website at <http://www.EUCAST.org>.

Citation of EUCAST documents

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This rationale document should be cited as: "European Committee on Antimicrobial Susceptibility Testing. Ceftolozane/Tazobactam: Rationale for the clinical breakpoints, version 1.0, 2019. <http://www.eucast.org>."

1. Introduction

Ceftolozane belongs to the cephalosporin class of antimicrobials. Ceftolozane exerts bactericidal activity through binding to important penicillin-binding proteins, resulting in inhibition of bacterial cell wall synthesis and subsequent cell death. Tazobactam is a beta-lactam structurally related to penicillins. It is an inhibitor of many molecular Class A beta-lactamases, including CTX-M, SHV, and TEM enzymes. Tazobactam does not exert any antibacterial activity but protects ceftolozane against hydrolysis.

The spectrum of activity for ceftolozane/tazobactam includes many clinically relevant gram-negative pathogens including *Pseudomonas aeruginosa*, *Enterobacterales*, such as *Escherichia coli* and *Klebsiella pneumoniae*, as well as *Haemophilus influenzae*.

Ceftolozane/tazobactam has a low potential for development of resistance in *P. aeruginosa* and *Enterobacterales*, including ESBL-producing strains. Bacterial resistance mechanisms that compromise ceftolozane/tazobactam include drug inactivation by serine carbapenemases, such as KPC, and metallo-beta-lactamases.

Ceftolozane/tazobactam is currently approved for the treatment of complicated intra-abdominal infections (cIAI), acute pyelonephritis (AP) and complicated urinary tract infections (cUTI), at a dose of 1.5 g (1 g/0.5 g) every 8 hours (q8h) by IV infusion over 1 hour in patients 18 years of age or older.

Clinical breakpoints have been determined for the use of ceftolozane/tazobactam for the treatment of nosocomial pneumonia (NP), including ventilator-associated pneumonia (VAP), when administered at a dose of 3 g q8h (twice the currently approved dose for the treatment of cIAI, AP and cUTI) by IV infusion over 1 hour for 8 to 14 days in patients 18 years of age or older.

2. Dosages

Standard dose schedule	Complicated intra-abdominal infections (cIAI), acute pyelonephritis (AP), and complicated urinary tract (cUTI) infections: 1 g ceftolozane / 0.5 g tazobactam q8h by IV infusion over 1 hour
Standard dose schedule for pneumonia	Nosocomial pneumonia, including ventilator-associated pneumonia (HAP/VAP): 2 g ceftolozane / 1 g tazobactam q8h by IV infusion over 1 hour
Available formulations	IV

3. MIC distributions and epidemiological cut-off (ECOFF) values (mg/L)

Updated MIC distributions and ECOFFs for both ceftolozane and ceftolozane-tazobactam can be found at <https://mic.eucast.org/Eucast2/SearchController/search.jsp?action=init>

Species	ECOFF
<i>Citrobacter freundii</i>	1
<i>Enterobacter cloacae</i>	1
<i>Escherichia coli</i>	1
<i>Haemophilus influenzae</i>	0.5
<i>Klebsiella aerogenes</i>	1
<i>Klebsiella oxytoca</i>	1
<i>Klebsiella pneumoniae</i>	1
<i>Morganella morganii</i>	1
<i>Proteus mirabilis</i>	1
<i>Pseudomonas aeruginosa</i>	4
<i>Serratia marcescens</i>	2
<i>Streptococcus agalactiae</i>	1
<i>Streptococcus pneumoniae</i>	0.5
<i>Streptococcus pyogenes</i>	0.5

4. Breakpoints prior to revision (mg/L) S_≤ / R_>

Not applicable

5. Pharmacokinetics			
Dosage (mg)	Ceftolozane/tazobactam 1500 mg (ceftolozane 1000 mg/tazobactam 500 mg) q8h by IV infusion over 1 hour in healthy subjects ¹	Ceftolozane/tazobactam 3000 mg (ceftolozane 2000 mg/tazobactam 1000 mg) q8h by IV infusion over 1 hour in healthy subjects ³	Ceftolozane/tazobactam 3000 mg (ceftolozane 2000 mg/tazobactam 1000 mg) or adjusted based on CrCL q8h by IV infusion over 1 hour in ventilated patients with suspected or confirmed pneumonia ⁴
Ceftolozane			
C _{max} (mg/L), mean (%CV)	74.4 (14)	112 (13)	110 (42)
C _{8h} (mg/L)	4.0 (39)	7.0 (24)	32.0 (73)
Total body clearance (L/h), mean (%CV)	5.6 (13)	6.7 (11)	5.4 (63)
t _{1/2} (h), mean (%CV)	3.12 (22)	2.8 (14)	5.7 (60)
AUC _{0-8h,ss} (mg.h/L) , mean (%CV)	182 (15)	300 (10)	448 (52)
Volume of distribution (L), mean (%CV)	14.2 (17)	17.9 (11)	32.1 (42)
Lung penetration ratio (%)	61 ²		50
Fraction unbound (%)	79 – 84		
Tazobactam			
C _{max} (mg/L), mean (%CV)	18.0 (8)	25.8 (15)	29.1 (47)
C _{8h} (mg/L)	0 (0, 0.16)	0.1 (0, 0.1)	2.87 (100)
Total body clearance (L/h), mean (%CV)	20.4 (14)	25.0 (12)	17.3 (66)
t _{1/2} (h), mean (%CV)	1.03 (19)	1.0 (18)	2.6 (58)
AUC _{0-8h,ss} (mg.h/L), mean (%CV)	25.0 (15)	40.5 (13)	74.0 (57)
Volume of distribution (L), mean (%CV)	17.9 (10)	24.6 (13)	43.3 (38)
Lung penetration ratio (%)	63 ²		62
Fraction unbound (%)	70		

Comments	<ul style="list-style-type: none"> • Cells are left empty when data are not available. • Protein binding for ceftolozane was determined in vitro using the ultrafiltration method. Protein binding for tazobactam was from the ZOSYN US prescribing information: Pfizer Inc., Nov 2018. • Lung penetration is calculated as the ratio of pulmonary epithelial lining fluid AUC and unbound plasma AUC using fraction unbound value of 79% for ceftolozane and 70% for tazobactam. • Tazobactam C8h in healthy subjects reported as median (minimum, maximum)
References	<ol style="list-style-type: none"> 1. Miller B, Hershberger E, Benziger D, Trinh M and Friedland I, <i>Antimicrob Agents Chemother</i> 2012; 56: 3086-91 and study report CXA-201-01 (data on file at Merck & Co., Inc., Kenilworth, New Jersey, USA) 2. Chandorkar G, Huntington JA, Gotfried MH, Rodvold KA, and Umeh O, <i>J Antimicrob Chemother</i> 2012; 67: 2463-69. 3. Yu B, Adedoyin A, Hershberger E, Caro L, Xiao A, Rhee EG and Huntington JA, <i>Clin Pharmacol Drug Development</i> 2018; 7: 382-91 and study report CXA-MD-11-07 (data on file at & Co., Yu B, Adedoyin A, Hershberger E, Caro L, Xiao A, Rhee EG and Huntington JA, <i>Clin Pharmacol Drug Development</i> 2018; 7: 382-91 and study report CXA-MD-11-07 (data on file at Merck & Co., Inc., Kenilworth, New Jersey, USA) 4. Caro L, Larson KB, Nicolau DP, De Waele J, Kuti JL, Saralaya R, Gadzicki E, Adedoyin A, Zeng Z and Rhee EG, P2225 ECCMID 21-24 April, 2018, Madrid, Spain, and study report of MK-7625A PN007 (data on file at Merck & Co., Inc., Kenilworth, New Jersey, USA)

6. Pharmacodynamics

Ceftolozane					
Animal data	Neutropenic murine thigh infection models				
	<i>Enterobacteriales</i> ¹		<i>Pseudomonas aeruginosa</i> ^{1, 2}		<i>Streptococcus pneumoniae</i> ²
Mean (Range) ± %CV	Wild Type	ESBL Producers	MIC ≤ 1 mg/L	MIC ≥ 2 mg/L	
fT>MIC for bacteriostasis	26.3 (24.0 – 28.1) (n=4 strains)	31.1 ± 4.4% (n=5 strains)	24.0 (21.4 – 28.5) (n=4 strains)	31.2 (15.9 – 40.1) (n=14 strains)	18.1 (12.6 – 25.4) (n=6 strains)
fT>MIC for 1 log reduction	31.6 (29.2 – 32.8) (n=4 strains)	34.8 ± 4.9% (n=5 strains)	31.5 (26.7 – 35.3) (n=4 strains)	39.4 (20.1 – 47.1) (n=12 strains)	23.8 (20.0 – 30.0) (n=6 strains)
fT>MIC for 2 log reduction	41.8 (40.8 – 43.4) (n=4 strains)		52.2 (35.5 – 66.0) (n=4 strains)	42.0 (27.6 – 46.5) (n=5 strains)	26.7 (25.9 – 27.7) (n=3 strains)
Tazobactam					
Animal data	Neutropenic murine thigh infection models				
	<i>Enterobacteriales</i> ³				
fT>C _T for bacteriostasis	20.3 (6.6 – 40.5) (n=6 strains) at C _T =1 mg/L				
fT>C _T for 1 log reduction	35.4 (17.4 – 45.2) (n=7 strains) at C _T =1 mg/L				
fT>C _T for 2 log reduction					
Clinical Data	None				
Comments	<ul style="list-style-type: none"> • Cells are left empty when data are not available. • The appropriate PK/PD index for efficacy of ceftolozane is fT>MIC; the appropriate PK/PD index of tazobactam is fT>C_T (a threshold concentration) • For Enterobacteriales, 2 <i>Escherichia coli</i> and 2 <i>Klebsiella pneumoniae</i> strains were studied in reference 1; 2 <i>Klebsiella pneumoniae</i> and 4-5 <i>Escherichia coli</i> strains were studied in reference 3 				

References

1. Craig WA and Andes DR, *Antimicrob Agents Chemother*, 2012; 57: 1577-82 and study report CXA.085.MC (data on file at Merck & Co., Inc., Kenilworth, New Jersey, USA).
2. Lepak AJ, Reda A, Marchillo K, Van Hecker J, Craig WA and Andes D, *Antimicrob Agents Chemother*, 2014; 58: 6311-14.
3. Melchers MJ, Maridou E, van Mil AC, Lagarde C and Mouton JW, *Antimicrob Agents Chemother*, 2016; 60: 7272-79 and study report CXA.83.MC (data on file at Merck & Co., Inc., Kenilworth, New Jersey, USA).

7. Monte Carlo simulations and PK/PD breakpoints

The probabilities of target attainment (PTA) for ceftolozane and tazobactam were evaluated using population PK models for Phase 1-3 studies at varying degrees of renal function using Monte Carlo simulation, based on doses of ceftolozane 1 g with tazobactam 0.5 g every 8 hours (1-hour infusion) for complicated intra-abdominal infections and complicated urinary tract infections, and doses ceftolozane 2 g with tazobactam 1 g every 8 hours (1-hour infusion) for nosocomial pneumonia. Reduced doses were models for patients with reduced renal function.

The PK/PD targets that were assessed for complicated intra-abdominal infections and complicated urinary tract infections included ceftolozane $fT > MIC$ of 24.8% for bacteriostasis, 32.2% for a 1- \log_{10} reduction in CFU and 40% for a 2- \log_{10} reduction, and a threshold concentration (C_T) of tazobactam of 1 mg/L as determined in the mouse thigh model.

Figure 1 Percentage achieving $fT > MIC$ for *Enterobacteriales*

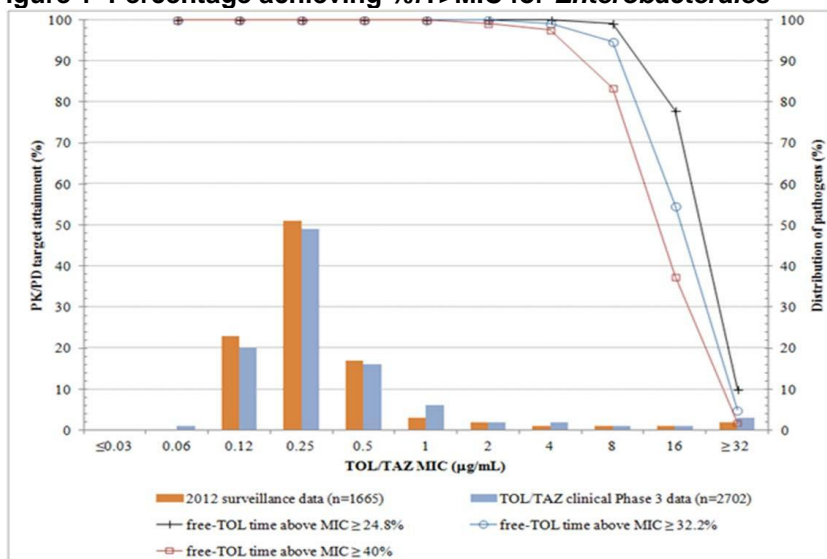
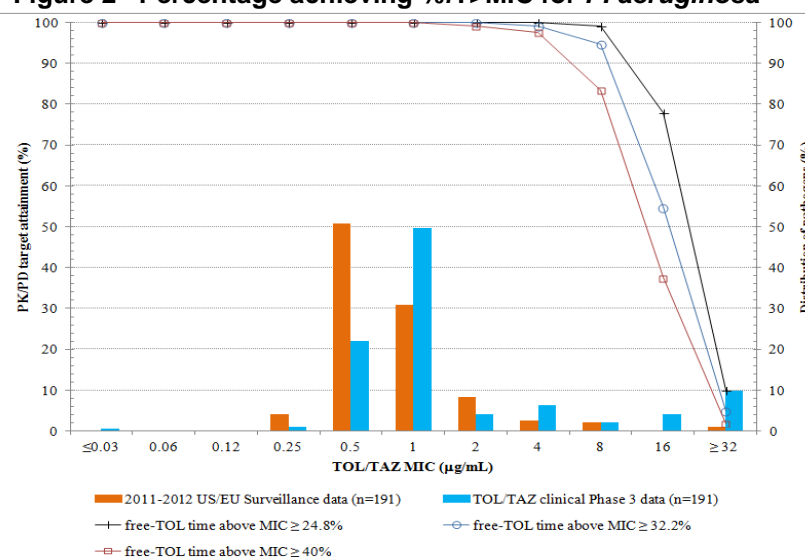


Figure 2 Percentage achieving $fT > MIC$ for *P. aeruginosa*



The PK/PD targets that were assessed for nosocomial pneumonia included ceftolozane $fT > MIC$ of 30% or a 1-log₁₀ reduction in CFU in both plasma and epithelial lining fluid Table 1, and a 20% $fT > C_T$ of tazobactam Table 2.

Table 1: Probability of Target Attainment for Ceftolozane of $fT > MIC$ at 30% in NP Patients Receiving Ceftolozane/Tazobactam Dosing Regimens Based on Renal Status

Renal Function		Percentage of Patients Achieving 30 % of $fT > MIC$													
		MIC (mg/L)	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	
15 mL/min ≤ CrCL ≤ 29 mL/min	500 mg TOL 250 mg TAZ	ELF	100	100	100	100	100	100	100	100	99.7	95.3	60.9	16.8	1.2
		Plasma	100	100	100	100	100	100	100	100	100	100	98	46.8	2.4
30 mL/min ≤ CrCL ≤ 50 mL/min	1000 mg TOL 500 mg TAZ	ELF	100	100	100	100	100	100	100	100	100	97.4	80.7	34.7	5.2
		Plasma	100	100	100	100	100	100	100	100	100	100	99.8	83	17.4
50 mL/min < CrCL < 80 mL/min	2000 mg TOL 1000 mg TAZ	ELF	100	100	100	100	100	100	100	100	100	99.6	93.4	56.9	15.6
		Plasma	100	100	100	100	100	100	100	100	100	100	100	97.7	45.8
ELF		100	100	100	100	100	100	100	100	100	100	98.1	79.6	33.8	5.7
Plasma		100	100	100	100	100	100	100	100	100	100	99.8	81.5	15.4	
ELF		100	100	100	100	100	100	100	100	100	99.9	95.4	64.7	19.3	1.3
Plasma		100	100	100	100	100	100	100	100	100	100	98.3	63.9	5.4	
ELF		100	100	100	100	100	100	100	100	100	99.4	92.6	56.7	12.5	0.8
Plasma		100	100	100	100	100	100	100	100	100	99.9	96.5	46.7	1.9	
ELF		100	100	100	100	100	100	100	100	100	99.2	88.3	49.5	9.9	0.5
Plasma		100	100	100	100	100	100	100	100	100	100	93.2	36.6	0.5	

Table 2: Probability of Target Attainment for Tazobactam of $fT > C_T = 1$ mg/L at 20% in NP Patients Receiving Ceftolozane/Tazobactam Dosing Regimens Based on Renal Status

Renal Function		Percentage of Patients Achieving 20 % of $fT > C_T = 1$ mg/L												
		C _T (mg/L)	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64
15 mL/min ≤ CrCL ≤ 29 mL/min	500 mg TOL 250 mg TAZ	ELF	100	100	100	100	98.5	87.2	53.4	18.4	2.6	0.2	0	0
		Plasma	100	100	100	100	100	100	98	63.8	13.6	0.7	0	0
30 mL/min ≤ CrCL ≤ 50 mL/min	1000 mg TOL 500 mg TAZ	ELF	100	100	100	100	99.8	96	73.1	31.7	5.3	0.5	0	0
		Plasma	100	100	100	100	100	100	99.1	88.9	35.3	2.5	0	0
50 mL/min < CrCL < 80 mL/min	2000 mg TOL 1000 mg TAZ	ELF	100	100	100	100	100	99	89.8	57.5	19.8	2.7	0.5	0
		Plasma	100	100	100	100	100	100	99.9	97.9	72.5	19.7	0.5	0
ELF		100	100	100	100	99.9	98.2	81.5	42.7	9	0.6	0	0	
Plasma		100	100	100	100	100	99.6	98.9	90.2	51.8	8	0.1	0	
ELF		100	100	100	100	99.5	94.3	70.6	27.4	4.9	0.3	0	0	
Plasma		100	100	100	100	99.9	99.5	97.4	82.5	32.6	2.1	0	0	
ELF		100	100	100	100	99.6	92.1	65	24.4	3.8	0	0	0	
Plasma		100	100	100	100	99.6	99.1	96.1	76.7	28.9	1.7	0	0	
ELF		100	100	100	100	99.3	92.3	62.1	20.5	1.9	0	0	0	
Plasma		100	100	100	100	100	98.3	93	71.6	20.9	0.2	0	0	

8. Clinical data

In complicated UTI, ceftolozane-tazobactam 1.5 g x 3 was compared to levofloxacin 750 mg x 1 in a phase 3 study. Microbiological outcomes by pathogen/pathogen group MIC are shown in Table 3. Overall, ceftazidime-tazobactam was non-inferior to meropenem.

Table 3: Pathogen Eradication Rates at TOC by Ceftolozane/Tazobactam MIC Value from the Phase 3 cUTI Study in the ME at TOC Population

Ceftolozane/ Tazobactam MIC (µg/mL)	Enterobacteriaceae n/N1 (%)	<i>E. coli</i> n/N1 (%)	<i>E. coli</i> (CTX-M-14/15) n/N1 (%)	<i>K. pneumoniae</i> n/N1 (%)	<i>K. pneumoniae</i> (CTX-M-14/15) n/N1 (%)	<i>P. mirabilis</i> n/N1 (%)	<i>P. aeruginosa</i> n/N1 (%)	<i>E. faecalis</i>
0.06	2/2 (100)	2/2 (100)	-	-	-	-	-	-
0.125	65/73 (89.0)	64/72 (88.9)	-	-	-	-	-	-
0.25	141/151 (93.4)	128/138 (92.8)	4/5 (80.0)	6/6 (100)	1/1 (100)	3/3 (100)	-	-
0.5	37/44 (84.1)	22/27 (81.5)	11/14 (78.6)	5/6 (83.3)	0/1 (0)	7/7 (100)	1/2 (50.0)	-
1	10/13 (76.9)	6/8 (75.0)	4/5 (80.0)	2/3 (66.7)	0/1 (0)	-	1/1 (100)	-
2	5/8 (62.5)	1/2 (50.0)	0/1 (0)	3/4 (75.0)	2/3 (66.7)	-	-	-
4	1/3 (33.3)	0/1 (0)	-	-	-	-	-	-
8	2/3 (66.7)	0/1 (0)	0/1 (0)	2/2 (100)	1/1 (100)	-	-	-
16	2/3 (66.7)	-	-	1/1 (100)	1/1 (100)	-	1/1 (100)	-
32	-	-	-	-	-	-	-	1/2 (50)
64	1/1 (100)	-	-	1/1 (100)	-	-	-	3/5 (60)
>64	2/5 (40.0)	1/2 (50.0)	0/1 (0)	-	-	-	2/2 (100)	1/8 (12.5)

In the Phase 3 trial in complicated intra-abdominal infections, ceftolozane-tazobactam plus metronidazole was compared to meropenem. Clinical cure rates by pathogen/pathogen group MIC are shown in Table 4. Overall, ceftazidime-tazobactam plus metronidazole was non-inferior to meropenem

Table 3: Clinical Cure Rates at TOC by Ceftolozane/Tazobactam MIC Value from the Phase 3 cIAI Study in the ME at TOC Population

Ceftolozane/ Tazobactam MIC (µg/mL)	Enterobacteriaceae n/N1 (%)	<i>C. freundii</i> n/N1 (%)	<i>E. coli</i> n/N1 (%)	<i>E. coli</i> (CTX-M-14/15) n/N1 (%)	<i>K. oxytoca</i> n/N1 (%)	<i>K. pneumoniae</i> n/N1 (%)	<i>P. mirabilis</i> n/N1 (%)	<i>E. cloacae</i> n/N1 (%)	<i>P. aeruginosa</i> n/N1 (%)
≤0.06	3/3 (100)	-	2/2 (100)	-	-	1/1 (100)	-	-	1/1 (100)
0.125	79/81 (97.5)	-	72/73 (98.6)	-	4/4 (100)	-	-	-	-
0.25	151/162 (93.2)	5/5 (100)	125/135 (92.6)	2/2 (100)	9/9 (100)	15/16 (93.8)	-	0/1 (0)	-
0.5	48/51 (94.1)	3/3 (100)	25/25 (100)	1/1 (100)	1/1 (100)	6/6 (100)	0/1 (0)	9/10 (90.0)	-
1	23/23 (100)	1/1 (100)	8/8 (100)	3/3 (100)	1/1 (100)	2/2 (100)	9/10 (90.0)	6/7 (85.7)	10/10 (100)
2	9/11 (81.8)	1/1 (100)	5/6 (83.3)	2/2 (100)	-	2/2 (100)	1/1 (100)	4/4 (100)	13/13 (100)
4	3/3 (100)	-	1/1 (100)	1/1 (100)	-	-	-	0/2 (0)	1/1 (100)
8	3/4 (75.0)	-	-	-	-	1/1 (100)	-	2/2 (100)	1/1 (100)
16	3/3 (100)	-	-	-	-	2/2 (100)	-	1/2 (50.0)	-
32	-	-	-	-	-	-	1/1 (100)	1/1 (100)	-
64	2/3 (66.7)	-	1/1 (100)	-	-	0/1 (0)	-	-	-
>64	1/1 (100)	-	1/1 (100)	-	-	-	-	1/1 (100)	-

In the Phase 4 trial in nosocomial pneumonia, ceftolozane-tazobactam was compared to meropenem. Clinical response rates by pathogen/pathogen group MIC are shown in Table 5.

Ceftolozane-tazobactam MIC (mg/L)	<i>P. aeruginosa</i> n/N (%)	<i>Enterobacterales</i>	<i>E. cloacae</i> n/N (%)	<i>E. coli</i> n/N (%)	<i>K. oxytoca</i> /N (%)	<i>K. pneumoniae</i> n/N (%)	<i>P. mirabilis</i> n/N (%)	<i>S. marcescens</i> n/N (%)	<i>H. influenzae</i> n/N (%)
≤0.06									3/3 (100)
0.125		10/16 (62.5)	1/2 (50.0)	4/7 (57.1)	2/3 (66.7)				10/11 (90.9)
0.25	1/2 (50.0)	45/74 (60.8)	3/5 (60.0)	18/27 (66.7)	6/9 (66.7)	8/18 (44.4)	3/4 (75.0)	1/1 (100)	5/6 (83.3)
0.5	15/24 (62.5)	34/51 (66.7)	3/6 (50.0)	5/8 (62.5)	1/1 (100)	12/14 (85.7)	8/13 (61.5)	5/6 (83.3)	1/2 (50.0)
1	7/12 (58.3)	14/23 (60.9)	1/2 (50.0)	5/6 (88.3)	0	6/8 (75.0)	0/2 (0.0)	1/3 (33.3)	
2	11/18 (61.1)	5/10 (50.0)	0	0	0/1 (0.0)	4/5 (80.0)	0/1 (0.0)	1/3 (33.3)	
4	2/3 (66.7)	8/15 (53.3)	0/1 (0.0)	0/2 (0.0)		5/7 (71.4)	2/2 (100)	0/1 (0.0)	
8	0/2 (0.0)	4/9 (44.4)	2/2 (100)	0.1 /0.0)		1/4 (25.0)	0/1 (0.0)	1/2 (50.0)	
16	0	3/8 (37.5)				3/7 (42.9)	1/2 (50.0)	0/1 (0.0)	
32	1/2 (50.0)	2/3 (66.7)				2/3 (66.7)			
64		7/9 (77.8)				7/8 (87.5)			
128		3/9 (33.3)				3/9 (33.3)			
≥256		2/3 (66.7)				2/3 (66.7)			

9. Clinical breakpoints

PK/PD breakpoints	S ≤4 mg/L, R >4 mg/L Based on a $fT > MIC$ target of 30% for ceftolozane and a ≥97% probability of target attainment and a $fT > C_{T=1}$ mg/L target of 20% for tazobactam and a ~97% probability of target attainment			
Species-related breakpoints	Organism group	MIC breakpoints (mg/L)		Notes
		S ≤	R >	
	<i>Enterobacterales</i> (all indications)	2	2	Breakpoints are the same for all registered indications even though the dosage for HAP/VAP is twice that of the other indications because this dosage results in same exposure in the lung that is seen with the dose used for other indications
	<i>Pseudomonas</i> spp. (all indications)	4	4	Breakpoints are the same for all registered indications even though the dosage for HAP/VAP is twice that of the other indications because this dosage results in same exposure in the lung that is seen with the dose used for other indications
	<i>Haemophilus influenzae</i> (HAP/VAP)	0.5	0.5	Based on highest MIC observed in the clinical study in HAP/VAP patients (PN008)
Clinical qualifications	None			
Dosage	A dose of 1.5 g q8h by IV infusion over 1 hour is for patients with cUTI, cIAI. A dose of 3 g q8h by IV infusion over 1 hour is for patients with HAP/VAP. The differing dosages ensure that exposure is the same at the different sites of infection.			
Additional comment	Microbroth dilution testing is performed with a fixed concentration of 4 mg/L of tazobactam.			

10. Exceptions noted for individual national committees

None.