

Rationale for EUCAST clinical breakpoints

Agent	Ceftobiprole	
Current version	1.0	31 March 2016
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. Ceftobiprole: Rationale for the clinical breakpoints, version 1.0 2016, <http://www.eucast.org>."

1. Introduction

Ceftobiprole is a cephalosporin agent, available only for parenteral use. The prodrug ceftobiprole medocaril sodium is converted *in vivo* to the microbiologically active ceftobiprole. Ceftobiprole has a high binding affinity for essential penicillin-binding proteins (PBPs) in many Gram-positive and Gram-negative bacteria, including PBP2a conferring methicillin-resistance in *Staphylococcus aureus*, PBP2x conferring penicillin-resistance in *Streptococcus pneumoniae* and PBP5 in *Enterococcus faecalis*.

Ceftobiprole is active *in vitro* against *S. aureus* (including the majority of MRSA), *S. pneumoniae* (including most penicillin-resistant isolates), and Enterobacteriaceae. Activity against *Pseudomonas aeruginosa* is moderate.. Ceftobiprole does not have useful activity against anaerobes, *Mycoplasma pneumoniae* or *Chlamydomphila pneumoniae*.

Resistance to ceftobiprole among staphylococcal and streptococcal isolates from surveillance and clinical studies is uncommon. Mechanisms of resistance to ceftobiprole among Enterobacteriaceae include expression of Ambler class A β -lactamases, particularly TEM, SHV and CTX-M extended-spectrum β -lactamases (ESBLs) and KPC-type carbapenemases, Ambler class B β -lactamases (metallo- β -lactamases), Ambler class D β -lactamases, especially ESBL variants and carbapenemases (OXA-48), and high levels of expression of Ambler class C β -lactamases. In *P. aeruginosa*, resistance is conferred by β -lactamases in Ambler class A (e.g., PSE-1), Ambler class B (e.g., IMP-1, VIM-1, VIM-2) and Ambler class D (e.g., OXA-10). Resistance in *P. aeruginosa* may also be conferred by mutations in regulatory genes leading to de-repression of expression of the chromosomal Ambler class C β -lactamase, or over-expression of the Mex XY efflux pump.

Ceftobiprole is approved by the MHRA for treatment of CAP and HAP (including VAP) in a dosage of 500mg as a 2 hour i.v. infusion every 8 h.

Clinical breakpoints have been determined for parenteral (iv) use of ceftobiprole in treating patients with pneumonia.

Information in this document is that available when the breakpoints were set in 2013, with more recent updating of the MIC distributions.

2. Dosage

Standard dose schedule	500mg as a 2 hour i.v. infusion x3
Maximum dose schedule	500mg as a 2 hour i.v. infusion x3
Available formulations	i.v.

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

Organism	0.002	0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	≥512	ECOFF
<i>Acinetobacter baumannii</i>	0	0	0	0	0	21	36	113	91	36	20	9	12	<u>617</u>	3	3	2	0	0	ND
<i>Acinetobacter pittii</i>	0	0	0	0	0	0	0	0	12	10	2	0	2	1	0	0	0	0	0	ND
<i>Acinetobacter</i> spp.	0	0	0	17	12	16	38	78	96	37	14	7	5	13	23	<u>108</u>	6	0	0	ND
<i>Citrobacter freundii</i>	0	0	0	25	66	11	1	7	10	11	8	0	0	4	1	0	0	0	0	ND
<i>Citrobacter koseri</i>	0	0	0	4	156	23	2	1	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Citrobacter</i> spp.	0	0	0	9	321	401	58	17	18	29	35	23	8	6	6	<u>31</u>	0	0	0	ND
<i>Clostridium difficile</i>	0	0	0	0	0	0	0	0	0	0	2	23	15	1	0	0	0	0	0	ND
<i>Enterobacter aerogenes</i>	0	0	0	57	193	189	39	13	2	7	2	1	1	<u>5</u>	<u>5</u>	1	0	0	0	0.12
<i>Enterobacter cloacae</i>	0	0	0	10	425	1176	381	138	59	58	99	143	95	<u>112</u>	<u>79</u>	<u>82</u>	<u>51</u>	4	0	0.25
<i>Enterococcus avium</i>	0	0	0	0	0	1	3	14	6	2	1	0	3	1	0	0	0	0	0	ND
<i>Enterococcus faecalis</i>	0	0	0	0	0	31	415	672	1371	462	271	110	72	<u>65</u>	0	0	0	0	0	ND
<i>Enterococcus faecium</i>	0	0	0	0	0	0	1	6	7	33	97	59	23	<u>1676</u>	<u>309</u>	<u>39</u>	0	0	0	ND
<i>Enterococcus gallinarum</i>	0	0	0	0	0	1	0	0	3	11	9	0	0	<u>9</u>	0	0	0	0	0	ND
<i>Escherichia coli</i>	0	0	4	682	4705	3328	785	193	72	37	23	27	29	<u>398</u>	<u>454</u>	<u>164</u>	<u>170</u>	19	2	0.25
<i>Haemophilus influenzae</i>	0	3	32	199	564	734	274	101	11	1	1	0	0	0	0	0	0	0	0	0.25
<i>Hafnia alvei</i>	0	0	0	0	0	3	10	6	3	0	2	2	2	2	2	0	0	0	0	ND
<i>Klebsiella oxytoca</i>	0	0	0	0	6	47	59	56	23	7	3	1	2	1	1	4	8	8	0	0.5
<i>Klebsiella pneumoniae</i>	0	0	1	222	867	1106	321	116	55	35	31	11	20	<u>364</u>	<u>484</u>	46	<u>102</u>	11	3	0.25
<i>Moraxella catarrhalis</i>	0	0	4	10	17	34	25	15	2	0	0	0	0	0	0	0	0	0	0	ND
<i>Morganella morganii</i>	0	0	0	44	172	80	6	2	2	0	1	0	0	1	6	0	0	0	0	0.12
<i>Proteus mirabilis</i>	0	0	2	346	2075	516	67	37	24	17	10	8	6	<u>21</u>	11	<u>13</u>	0	0	0	0.12
<i>Pseudomonas aeruginosa</i>	0	0	0	1	4	11	11	81	496	2748	3168	1904	1682	<u>1572</u>	285	<u>170</u>	0	1	0	8
<i>Raoultella ornithinolytica</i>	0	0	0	0	0	7	15	15	15	5	3	1	2	0	0	11	<u>9</u>	0	0	ND

<i>Serratia liquefaciens</i>	0	0	0	0	7	12	0	1	0	0	0	0	0	0	1	0	0	0	0	ND
<i>Serratia marcescens</i>	0	0	1	1	45	537	300	81	50	25	8	11	7	<u>11</u>	23	<u>25</u>	0	0	0	1
<i>Staphylococcus aureus</i> MSSA	0	0	0	0	0	71	393	10568	7029	430	12	0	0	0	0	0	0	0	0	1
<i>Staphylococcus aureus</i> MRSA	0	0	0	0	1	9	14	109	4313	9329	3012	210	1	3	0	0	0	0	0	1
<i>Staphylococcus aureus</i>	0	0	0	1	3	176	725	21825	20003	15877	5405	333	2	6	0	0	0	0	0	1
<i>Staphylococcus epidermidis</i> MSSE	0	0	0	1	1	0	14	42	20	4	2	0	0	0	0	0	0	0	0	ND
<i>Staphylococcus epidermidis</i> MRSE	0	0	0	0	0	0	0	0	28	102	15	0	0	0	0	0	0	0	0	ND
<i>Staphylococcus epidermidis</i>	0	0	0	1	0	50	317	347	846	1028	193	64	0	0	0	0	0	0	0	ND
<i>Staphylococcus haemolyticus</i>	0	0	0	0	0	7	15	36	48	87	123	186	11	0	0	0	0	0	0	ND
<i>Staphylococcus hominis</i>	0	0	0	0	0	8	47	47	31	116	73	22	0	0	0	0	0	0	0	ND
<i>Staphylococcus lugdunensis</i>	0	0	0	0	0	4	6	7	58	10	0	1	0	0	0	0	0	0	0	ND
<i>Staphylococcus saprophyticus</i>	0	0	0	0	0	0	1	11	22	4	1	1	0	0	0	0	0	0	0	ND
<i>Staphylococcus warneri</i>	0	0	0	0	0	4	28	36	20	11	3	5	0	0	0	0	0	0	0	ND
<i>Staphylococcus xylois</i>	0	0	0	0	0	0	3	2	16	11	0	2	0	0	0	0	0	0	0	ND
<i>Streptococcus agalactiae</i>	0	2	5	144	718	87	2	1	0	0	0	0	0	0	0	0	0	0	0	0.06
<i>Streptococcus anginosus</i>	0	0	0	3	5	46	111	18	3	0	0	0	0	0	0	0	0	0	0	0.25
<i>Streptococcus</i> group G	0	14	192	147	18	3	1	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus oralis</i>	0	0	12	72	149	43	54	32	19	11	4	2	1	0	0	0	0	0	0	0.12
<i>Streptococcus pneumoniae</i>	46	77	1491	3356	620	391	306	563	683	154	18	1	0	0	0	0	0	0	0	0.03
<i>Streptococcus pyogenes</i>	0	19	266	58	14	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.03
<i>Streptococcus sanguinis</i>	0	0	0	5	9	1	2	0	0	0	0	0	0	0	0	0	0	0	0	ND

The table includes MIC distributions available at the time breakpoints were set, and updated in March 2016. They represent combined distributions from multiple sources and time periods. The distributions are used to define the epidemiological cut-off values (ECOFF) and give an indication of the MICs for organisms with acquired resistance mechanisms. They should not be used to infer resistance rates. The MIC distributions at the underlined numbers are distorted by truncation of some aggregated distributions. When there is insufficient evidence or when the species has not been identified to species level the ECOFF has not been determined (ND). The ECOFF is not affected by the presence of resistance mechanisms; so distributions composed entirely of isolates with specific resistance mechanisms or mixtures of isolates with and without resistance mechanisms have the same ECOFF as the population of the same species with no resistance mechanisms.

4. Breakpoints prior to harmonisation (mg/L) S≤ / R>							
	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA	CLSI
General breakpoints	No previous breakpoints						
Species-related breakpoints	No previous breakpoints						
Enterobacteriaceae							
<i>Pseudomonas</i> spp.							
<i>Stenotrophomonas maltophilia</i>							
<i>Acinetobacter</i> spp.							
<i>Staphylococcus</i> spp.							
<i>Enterococcus</i> spp.							
Streptococcus groups A,B,C,G							
<i>Streptococcus pneumoniae</i>							
Viridans group streptococci							
<i>Haemophilus influenzae</i>							
<i>Moraxella catarrhalis</i>							
<i>Neisseria gonorrhoeae</i>							
<i>Neisseria meningitidis</i>							
Anaerobes, Gram-positive							
<i>Clostridium difficile</i>							
Anaerobes, Gram-negative							
<i>Helicobacter pylori</i>							
<i>Listeria monocytogenes</i>							
<i>Pasteurella multocida</i>							
<i>Campylobacter</i> spp.							
<i>Corynebacterium</i> spp.							

5. Pharmacokinetics

Dosage (mg)	Single dose (Day 1) 500 mg 2 hour i.v. infusion Mean Value (SD)	Multiple doses (Day 5 – steady state) 500 mg 2 hour i.v. infusion x 3 Mean Value (SD)		
C _{max} (mg/L)	29.2 (5.52)	33.0 (4.83)		
C _{min} (mg/L)	3.06 (0.482)	3.34 (0.739)		
Total body clearance (L/h)	4.89 (0.69)	4.98 (0.58)		
T _½ (h), mean (range)	3.1 (0.3)	3.3 (0.3)		
AUC _{24h} (mg.h/L)	104 (13.9)	102 (11.9)		
AUC _{0-12h,ss} (mg.h/L)				
AUC _∞ (mg.h/L)				
Fraction unbound (%)	84	84		
Volume of distribution (L/kg)	21.7 (3.37)	15.5 (2.33)		
Comments	- Cells are left empty when data are not available. - C_{min} on Day 1 is C_{last} and on Day 5 is pre-dose concentration or C_{trough} - AUC on Day1 is AUC_{0-∞} and on Day 5 is AUC_{0-8h} - Protein binding is independent of drug and protein concentration			
References	- Murthy B, Schmitt-Hoffmann A. Pharmacokinetics and pharmacodynamics of ceftobiprole, an anti-MRSA cephalosporin with broad-spectrum activity. <i>Clin Pharmacokinet.</i> 2008; 47: 21-33. - Kimko H, Murthy B, Xu X, Nandy P, Strauss R, Noel GJ. Population pharmacokinetic analysis of ceftobiprole for treatment of complicated skin and skin structure infections. <i>Antimicrob Agents Chemother.</i> 2009; 53:1228-30.			

6. Pharmacodynamics

Animal data	Murine thigh and lung infection models.			
	<i>S. aureus</i>	<i>S. pneumoniae</i>	Enterobacteriaceae, <i>P. aeruginosa</i>	
$fT > MIC$ for bacteriostasis	8 – 15	15-22	36-45	
$fT > MIC$ for 1 log reduction	10-20	-	-	
$fT > MIC$ for 2 log reduction	23 - 29%	19-30	41-100	
Clinical Data	30-60		50-60	
Comments	- Cells are left empty when data are not available. - The appropriate PK-PD index for efficacy of ceftobiprole is $fT > MIC$ - Sixteen <i>S. aureus</i> (6 MSSA and 10 MRSA) tested in murine thigh and lung infection models (Craig and Andes, 2008; Laohavaleeson et al, 2008; Rodvold et al, 2009) - Six <i>S. pneumoniae</i> tested in murine thigh infection model (Craig and Andes 2008) - One <i>E. coli</i>, 1 <i>K. pneumoniae</i>, 2 <i>E. cloacae</i>, and 1 <i>P. aeruginosa</i> tested in murine thigh infection model (Craig and Andes 2008) - Clinical data derived from studies of complicated skin and skin structure infections (Kimko et al, 2009) and nosocomial pneumonia (Muller et al, 2014)			
References	- Craig WA, Andes DR, <i>Antimicrob Agents Chemother</i> 2008; 52: 3492-96. - Laohavaleeson S, Tessier PR, and Nicolau D. <i>Antimicrob Agents Chemother</i> 2008; 52: 2389–94. - Rodvold KA, Nicolau DP, Lodise, TP, et al. <i>Antimicrob Agents Chemother</i> 2009; 53: 3294–3301. - Muller A, Punt N, Mouton JW. <i>Antimicrob Agents Chemother</i> 2014; 58: 2512-19 - Kimko H, Xu X, Nandy P et al. <i>Antimicrob Agents Chemother</i> 2009; 54: 953-55			

7. Monte Carlo simulations and PK/PD breakpoints

The probabilities of target attainment were obtained by Monte Carlo simulations using a population PK model developed for unbound ceftobiprole (unbound fraction of 0.84) based on data from six studies, three Phase 1 studies of healthy male and female subjects, including some with renal impairment, one Phase 1 study of ICU patients, one Phase 2 study of patients with complicated skin and soft tissue infection and one Phase 3 study of patients with nosocomial pneumonia. The pooled data are best described by a 3-compartment model (Muller et al, *Antimicrob Agents Chemother* 2013; 57: 2047-53 and *Antimicrob Agents Chemother* 2014; 58: 2512-19). Percentage Target Attainment for patients enrolled in the Phase 3 nosocomial pneumonia trial receiving ceftobiprole 500 mg as a 2h infusion every eight hours are shown in figure 1.

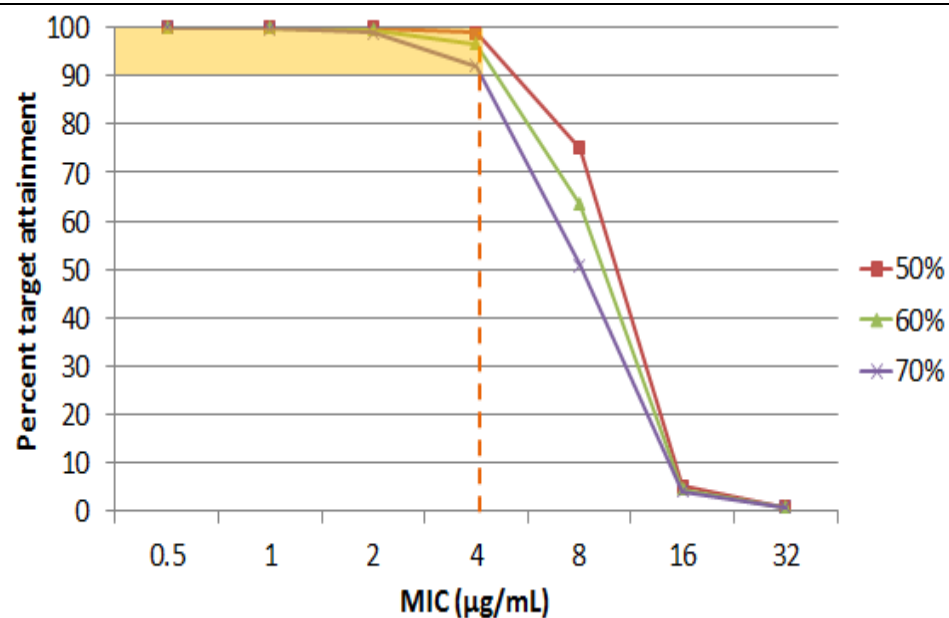


Figure 1. Probabilities of target attainment for ceftobiprole 500 mg as a 2h i.v. infusion every 8 hours.

Probabilities of target attainment are shown for $fT > MIC$ targets of 50%, 60% and 70%.

A $fT > MIC$ target of 50% and a $>90\%$ target attainment rate results in a susceptible PK-PD breakpoint of 4 mg/L for a dosage of ceftobiprole 500 mg as a 2 h i.v. infusion every 8 h. There is no higher dose so the resistant PK-PD breakpoint is >4 mg/L.

Probability of Target Attainment (PTA), based on a target of 50% $fT > MIC$ for a target of 4 mg/L, from two Monte Carlo simulations are shown below.

Study	Target	Dosing regimen	PTA (MIC of 4 µg/mL)	Source data [number patients receiving ceftobiprole]
Mouton, 2004	50% $fT > MIC$	500 mg x 3 (30min infusion)	99%	Phase I MAD study [12 subjects]
Lodise, 2008	50% $fT > MIC$	500 mg x 3 (2h infusion)	80%	Numerous Phase 1 studies, including renal impairment study [150 subjects] Phase 2 complicated skin and soft tissue infection study [27 subjects]

8. Clinical data

Ceftobiprole was studied in two double-blinded randomized, global, multi-centre clinical studies comparing the efficacy and safety of ceftobiprole as a 500 mg 2h i.v. infusion every eight hours versus a comparator regimen to treat hospitalized patients with pneumonia who required intravenous antibacterial therapy. The predefined primary endpoint used in both studies was clinical cure at “test of cure”, with “test of cure” defined as 7-14 days following end of therapy.

In a randomised, double-blind trial comparing ceftobiprole with ceftriaxone with or without linezolid for the treatment of patients with community-acquired pneumonia and requiring hospitalisation, 638 patients were randomised into two study arms. 314 patients were treated with ceftobiprole as a 500mg 2h i.v. infusion every eight hours and 324 patients were treated with ceftriaxone as a 2g 30 min i.v. infusion every 24 hours +/- linezolid as a 600mg 1h i.v. infusion every 12 hours (Nicholson SC et al. *Int J Antimicrob Agents* 2012; 39: 240-6).

In a phase 3 randomized double-blind comparison of ceftobiprole versus ceftazidime plus linezolid for the treatment of hospital-acquired pneumonia 781 patients were randomised into two study arms. 391 patients were treated with ceftobiprole as a 500mg 2h i.v. infusion every eight hours and 390 patients were treated with ceftazidime as a 2g 2h i.v. infusion every eight hours plus linezolid as a 600mg 1h i.v. infusion every 12 hours. In both study arms combination therapy with agents predefined in the protocol (levofloxacin, amikacin or gentamicin) was permitted patients identified as at risk of pseudomonal infections (Awad SS et al. *Clin Infect Dis*. 2014; 59: 51-61).

Both studies met the predefined endpoints demonstrating ceftobiprole to be non-inferior to comparator agents with a predefined non-inferiority margin of 10% for community acquired pneumonia and 15% for nosocomial pneumonia.

The most common pathogens encountered at baseline from patients enrolled in the pneumonia study were *S. aureus* (including MRSA), *S. pneumoniae* (including penicillin-non-susceptible isolates), *E. coli*, *K. pneumoniae* and *P. aeruginosa*.

9. Clinical breakpoints

PK/PD breakpoints	PK/PD breakpoints have been determined using PK/PD data and are independent of MIC distributions of specific species. They are for use only as a guide for organisms that do not have specific breakpoints. PK/PD breakpoints have been termed “non-species-related breakpoints” but this has led to confusion and it has become clear that PK/PD breakpoints for some agents may differ for different organisms.			
	A fT>MIC target of 50% and a >90% target attainment rate results in a susceptible breakpoint of 4 mg/L for a dosage of ceftobiprole 500 mg as a 2 h i.v. infusion every 8 h. There is no higher dose so the resistant breakpoint is >4 mg/L.			
Species-related breakpoints	Organism group	MIC breakpoints (mg/L)		Notes
		S ≤	R >	
	Enterobacteriaceae	0.25	0.25	1. The breakpoints were reduced from S ≤ 4, R >4 mg/L to S ≤ 0.25, R >0.25 mg/L as evidence of clinical efficacy for Enterobacteriaceae with MICs >0.25 mg/L is very poor.
	<i>Pseudomonas</i> spp.	IE	IE	2. There is insufficient evidence that the species in question is a good target for therapy with the agent.
	<i>Stenotrophomonas maltophilia</i>	-	-	3. These organisms were considered poor targets for therapy or inappropriate targets for the specified infections and for that reason did not receive breakpoints.
	<i>Acinetobacter</i> spp.	-	-	See note 3.
	<i>Staphylococcus</i> spp.	2	2	4. The breakpoints were reduced from S ≤ 4, R >4 mg/L to S ≤ 2, R >2 mg/L because MICs for many MRSA are slightly raised compared with wild type isolates, there is no clinical evidence supporting breakpoints above 2 mg/L and isolates with confirmed ceftobiprole MICs >2mg/L are currently uncommon.
	<i>Enterococcus</i> spp.	-	-	See note 3.
	Streptococcus groups A,B,C,G	IE	IE	See note 2.
	<i>Streptococcus pneumoniae</i>	0.5	0.5	5. The breakpoints were reduced from S ≤ 4, R >4 mg/L to S ≤ 0.5, R >0.5 mg/L. because evidence of clinical efficacy against <i>Streptococcus pneumoniae</i> with MICs >0.5 mg/L is very poor.
	Viridans group streptococci	-	-	See note 3.
	<i>Haemophilus influenzae</i>	IE	IE	See note 2.
	<i>Moraxella catarrhalis</i>	IE	IE	See note 2.
	<i>Neisseria gonorrhoeae</i>	-	-	See note 3.
	<i>Neisseria meningitidis</i>	-	-	See note 3.
	Anaerobes, Gram-positive	-	-	See note 3.
	<i>Clostridium difficile</i>	-	-	See note 3.
	Anaerobes, Gram-negative	-	-	See note 3.
	<i>Helicobacter pylori</i>	-	-	See note 3.
	<i>Listeria monocytogenes</i>	-	-	See note 3.

	<i>Pasteurella multocida</i>	-	-	See note 3.
	<i>Campylobacter</i> spp.	-	-	See note 3.
	<i>Corynebacterium</i> spp.	-	-	See note 3.
Clinical qualifications				
Dosage	500mg as a 2 h i.v. infusion every 8 h.			
Additional comment				

10. Exceptions noted for individual national committees
None.