



EUCAST

EUROPEAN COMMITTEE
ON ANTIMICROBIAL
SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Mecillinam

Rationale for the EUCAST clinical breakpoints, version 1.0

22nd November 2010

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 document

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

Citation of EUCAST documents

This rationale document should be cited as: "European Committee on Antimicrobial Susceptibility Testing. Mecillinam: Rationale for the clinical breakpoints, version 1.0, 2010. <http://www.eucast.org>.

Introduction

Mecillinam is an amidinopenicillin. It is administered orally as pivmecillinam, which is hydrolysed to the active drug, mecillinam in vivo.

Mecillinam is active against many Gram-negative bacteria but *Acinetobacter* spp. and Gram-positive bacteria are commonly resistant or activity is poor. Resistance may arise following permeability changes or due to production of certain beta-lactamases.

Mecillinam is considered relevant only for therapy of uncomplicated urinary tract infections caused by *E. coli*, *Klebsiella* spp. and *P. mirabilis*. Clinical experience with mecillinam in the treatment of infections caused by bacteria other than *E. coli*, *Klebsiella* spp. and *P. mirabilis* is very limited.

1. Dosage

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose	200 mg x 3	200 mg x 3 400 mg x 2	-	-	200-400 mg x 3	200 mg x 3
Maximum dose schedule	400 mg x 4	400 mg x 4	-	-	400 mg x 4	400 mg x 3
Available formulations	Oral	Oral	-	-	Oral	Oral

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

	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
<i>Acinetobacter</i> spp.	0	0	79	9	10	10	53	10	20	9	19	28	56	50	70	77	162	179	0	ND
<i>Citrobacter freundii</i>	0	0	1	1	0	1	0	0	0	0	0	1	4	0	3	1	0	0	0	ND
<i>Citrobacter koseri</i>	0	0	0	0	0	0	6	2	169	22	17	25	31	20	9	6	37	1	3	ND
<i>Citrobacter</i> spp.	0	0	0	17	2	0	29	7	700	225	176	267	373	453	345	436	1697	118	25	ND
<i>Enterobacter aerogenes</i>	0	0	0	0	0	0	0	0	3	1	8	0	0	1	0	0	0	1	0	ND
<i>Enterobacter cloacae</i>	0	0	0	0	0	0	1	1	12	4	6	1	2	1	0	0	1	1	0	ND
<i>Enterobacter</i> spp.	0	0	0	0	0	41	238	275	109	54	56	34	26	3	3	2	1	0	0	1
<i>Escherichia coli</i>	0	0	2	3	7	118	215	335	202	160	241	228	183	82	34	23	7	22	8	1
<i>Klebsiella pneumoniae</i>	0	0	0	0	0	0	0	0	0	0	1	4	3	11	3	0	0	3	0	ND
<i>Morganella morganii</i>	0	0	0	1	0	0	1	6	18	14	6	11	5	10	5	3	5	1	1	ND
<i>Proteus mirabilis</i>	0	0	0	0	0	0	0	0	0	0	2	0	4	4	0	1	0	0	0	ND
<i>Proteus vulgaris</i>	0	0	0	0	0	0	0	0	0	0	1	3	10	1	2	0	2	0	0	ND
<i>Providencia</i> spp.	0	0	0	0	0	1	0	0	62	294	777	234	142	142	120	160	135	24	36	8
<i>Providencia stuartii</i>	0	0	0	0	0	1	0	1	14	68	370	90	48	22	3	4	3	1	0	8
<i>Pseudomonas aeruginosa</i>	0	0	0	0	0	4	0	0	4	121	313	79	80	34	17	18	12	9	43	8
<i>Salmonella</i> spp.	0	0	11	24	33	17	2	3	0	3	1	0	2	0	0	0	0	0	0	0.125
<i>Serratia liquefaciens</i>	0	0	0	0	0	0	0	0	2	0	0	1	0	1	7	0	18	2	5	ND
<i>Serratia marcescens</i>	0	0	0	0	2	0	2	5	43	238	1006	624	297	329	417	327	144	70	53	8
<i>Staphylococcus saprophyticus</i>	0	0	0	0	0	0	0	3	25	20	5	5	0	0	0	0	0	0	0	ND
<i>Stenotrophomonas maltophilia</i>	0	0	0	2	9	15	42	166	669	1582	4020	1560	665	526	663	776	961	146	87	8
<i>Yersinia enterocolitica</i>	0	0	0	0	0	0	0	0	1	4	24	4	2	1	2	0	0	0	0	8

The table includes MIC distributions available at the time breakpoints were set. They represent combined distributions from multiple sources and time periods. The distributions are used to define the epidemiological cut-offs (ECOFF) and give an indication of the MICs for organisms with acquired or mutational resistance mechanisms. They should not be used to infer resistance rates. When there is insufficient evidence no epidemiological cut-off has been determined (ND).

3. Breakpoints prior¹ to harmonisation (mg/L) S_≤ R_{>}							
	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA	CLSI²
General breakpoint							
						1/8	
Species specific breakpoints:							
Enterobacteriaceae	8/8	2/8			2/8	1/8	8/16
<i>Pseudomonas</i> spp.							
<i>Acinetobacter</i> spp.							
<i>Staphylococcus</i> spp.							
<i>Streptococcus</i> spp.							
Alpha haemolytic streptococci							
<i>Streptococcus pneumoniae</i>							
<i>Enterococcus</i> spp.							
<i>Haemophilus influenzae</i>							
<i>Moraxella catarrhalis</i>							
Corynebacteria							
<i>Neisseria meningitidis</i>							
<i>Neisseria gonorrhoeae</i>							
<i>Pasteurella multocida</i>							
Anaerobes, Gram-positive							
Anaerobes, Gram-negative							
<i>Campylobacter</i> spp.							
<i>Helicobacter pylori</i>							

¹2005

²CLSI breakpoints converted to EUCAST terminology.

4. Pharmacokinetics					
Dosage (mg)	200 x 1	400 x 1			
Bioavailability	60-75%	60-75%			
Cmax (mg/L)	3.5	176-1324 (urine)			
Cmin (mg/L) 6 hr					
Total body clearance (L/g/h)					
T ½ (h), mean (range)	0.7 - 1	1.79 (urine)			
AUC24h (mg.h/L)					
Fraction unbound (%)	90 - 95				
Volume of distribution (L/kg)	0.2 – 0.4				
Comments	<ul style="list-style-type: none"> • Pharmacokinetic data are based on a single dose. • Two values are given where references differ. Cells are left empty when data are not readily available. • Oral absorption is c. 75 %, Approximately 60 % is excreted unchanged in urine in the first 6h • No active metabolites 				
References	<ul style="list-style-type: none"> • Kern MB et al. <i>Clin Microbiol Infect</i> 2004;10;54-61 • Bryskier. Penicillins. In <i>Antimicrobial Agents</i> 2005; pp113-162 				

5. Pharmacodynamics

	Enterobacteriaceae				
%fT>MIC for stasis : exp	30 – 35				
%fT>MIC for 2 log drop : exp					
%fT>MIC from clinical data					
Comments	<ul style="list-style-type: none"> • Cells are left empty when data are not readily available. • Mecillinam is used only for lower urinary tract infections • Urine concentrations are sufficiently high to meet the pharmacodynamic target in strains with MICs of ≤ 8 mg/L • Mecillinam is moderately stable to many Gram-negative beta-lactamases including many extended-spectrum beta-lactamases. No clinical trials have been carried out in patients with infections caused by ESBL-producing <i>E.coli</i>. 				
References	<ul style="list-style-type: none"> • Kern M.B. et al, <i>Clin Microbiol Infect</i> 2004;10: 54-61 				

6. Monte Carlo simulations and PK/PD Breakpoints

Not available.

7. Clinical data

Mecillinam has been shown to be well tolerated and give a bacteriological cure rate in uncomplicated urinary tract infection of >85 % with the treatment schedule of 400 mg x 2 for 3 days; and similar clinical cure rates to norfloxacin (400 mg x2 for 3 days) when given at a dose of 200 mg x 2 for 7 days.

- Nicolle LE et al. *J Antimicrob Chemother* 2000; 46, Suppl. S1: 35-39

8. Clinical breakpoints

Non-species-related breakpoints	There is insufficient evidence to set non-species-related breakpoints.
Species-related breakpoints	Breakpoints were based on pharmacokinetic data, microbiological data and clinical experience. Concentrations in urine are high enough to provide an appropriate $fT > MIC$ in urine. For <i>E. coli</i> , <i>Klebsiella</i> spp. and <i>P. mirabilis</i> breakpoints are $S \leq 8$ mg/L / $R > 8$ mg/L.
Species without breakpoints	<i>Pseudomonas aeruginosa</i> , <i>Acinetobacter</i> spp., <i>Staphylococcus</i> spp., <i>Enterococcus</i> spp., streptococci, <i>Haemophilus influenzae</i> , <i>Moraxella catarrhalis</i> , <i>Neisseria</i> spp. and anaerobes were considered poor targets or inappropriate for mecillinam therapy and for that reason did not receive breakpoints.
Clinical qualifications	Breakpoints are valid only for uncomplicated urinary tract infection.
Dosage	Breakpoints apply to an oral dose of 200-400 mg x 3.
Additional comment	

9. EUCAST clinical MIC breakpoints

All EUCAST breakpoints can be found at <http://www.eucast.org>

10. Exceptions noted for individual national committees

None