

**Fosfomycin trometamol**

**Rationale for the EUCAST clinical breakpoints, version 1.0**

15<sup>th</sup> February 2013

## 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. Fosfomycin trometamol: Rationale for the clinical breakpoints, version 1.0, 2013. <http://www.eucast.org>.

## Introduction

Fosfomycin trometamol is a derivative of fosfomycin for oral use in uncomplicated urinary tract infections, primarily infections caused by *Escherichia coli*. The clinical efficacy in this indication is well documented. Despite this, only few European countries have a tradition of using fosfomycin trometamol. The fact that the majority of extended-spectrum-beta-lactamase (ESBL) producing *E. coli* and other multiresistant *E. coli* isolates are still without resistance mechanisms to fosfomycin has led to an increased interest in the drug. Nevertheless, it has been recently described the emergence of fosfomycin resistance in widely distributed ESBL producing *E. coli* clones.

Fosfomycin is a rapid bactericidal broad spectrum agent that inhibits cell wall synthesis by irreversibly inhibiting enolpyruvyl transferase catalyzing the first step in the biosynthesis of peptidoglycan.

## 1. Dosage

	<b>BSAC</b>	<b>CA-SFM</b>	<b>CRG</b>	<b>DIN</b>	<b>NWGA</b>	<b>SRGA</b>
Most common dose	3g x 1	3g x 1	3g x 1	3g x 1	-	3g x 1
Maximum dose schedule	3g x 1	3g x 1	3g x 1	3g x 1	-	3g x 1
Available formulations	Oral	Oral	Oral	Oral	-	Oral

## 2. MIC distributions and epidemiological cut-off (ECOFF) values

	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	0	0	0	0	0	1	0	1	1	0	0	7	6	21	31	18	0	ND
<i>Citrobacter</i> spp	0	0	0	0	0	6	38	2	2	2	1	0	0	0	0	0	0	0	0	ND
<i>Enterobacter aerogenes</i>	0	0	0	0	0	0	0	0	0	0	1	2	7	19	32	13	6	0	0	ND
<i>Enterobacter cloacae</i>	0	0	0	0	0	0	0	0	0	0	3	23	13	18	24	75	105	0	0	ND
<i>Enterobacter</i> spp	0	0	0	0	0	0	0	0	8	14	6	11	29	69	35	16	18	21	5	ND
<i>Enterococcus faecalis</i>	0	0	0	0	0	0	0	0	2	2	0	1	17	98	959	502	64	9	12	ND
<i>Enterococcus faecium</i>	0	0	0	0	0	0	0	0	1	0	0	0	0	3	54	373	52	0	0	ND
<i>Enterococcus</i> spp	0	0	0	0	0	0	0	1	0	0	0	0	8	46	31	6	3	1	0	ND
<i>Escherichia coli</i>	0	0	0	0	1	1	54	74	513	890	922	1013	801	483	243	89	33	0	0	8
<i>Haemophilus influenzae</i>	0	0	0	0	0	0	0	0	0	37	5	5	0	0	1	1	1	0	0	ND
<i>Klebsiella</i> spp	0	0	0	0	0	0	6	3	27	50	47	73	138	147	127	64	25	16	35	ND
<i>Proteus mirabilis</i>	0	0	0	0	0	0	6	15	89	188	200	199	242	100	78	88	89	34	0	8
<i>Proteus</i> spp	0	0	0	0	0	0	0	0	17	23	30	20	37	37	36	29	14	16	23	ND
<i>Providencia</i> spp	0	0	0	0	0	0	1	2	2	2	24	15	5	1	2	0	0	0	0	ND
<i>Pseudomonas aeruginosa</i>	0	0	0	0	0	0	0	0	8	4	32	46	58	100	174	350	216	14	22	ND
<i>Serratia marcescens</i>	0	0	0	0	0	0	0	0	3	7	20	51	30	36	7	6	4	0	0	ND
<i>Shigella</i> spp	0	0	0	0	0	0	0	0	4	63	101	8	6	0	0	3	0	0	0	ND
<i>Staphylococcus aureus</i>	0	0	0	0	0	0	2	2	91	226	389	366	465	309	121	50	25	2	3	32
<i>Staphylococcus epidermidis</i>	0	0	0	0	0	0	0	0	49	116	135	95	141	100	30	47	182	1	0	ND
<i>Staphylococcus saprophyticus</i>	0	0	0	0	0	0	0	0	0	0	0	2	0	2	7	23	5	10	0	ND
<i>Streptococcus pneumoniae</i>	0	0	0	0	0	0	0	0	0	0	0	16	32	6	3	0	0	0	0	ND
<i>Streptococcus pyogenes</i>	0	0	0	0	0	0	0	0	0	0	1	0	1	3	25	20	0	0	0	ND

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 prior to harmonisation (mg/L) S ≤ R >

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA	CLSI
<b>General breakpoint</b>							
		32/32					
<b>Species specific breakpoints:</b>							
Enterobacteriaceae	128/128 <i>E coli</i> UTI	32/32				16/64 <i>E coli</i>	64 /128 <i>E. coli</i> UTI
<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>							

<b>4. Pharmacokinetics</b>				
Dosage (mg)	3 g oral (fosfomycin trometamol)			
Bioavailability				
Cmax (mg/L)	22-32 serum 4415 urine			
Cmin (mg/L)				
Total body clearance (L/h)	7.2			
T ½ (h), mean (range)	2.4-7.3			
AUC24h (mg.h/L)	145-228			
Fraction unbound (%)	>97%			
Volume of distribution (L/kg)				
Comments	<ul style="list-style-type: none"> <li>• Cells are left empty when data are not readily available. Two values are given where references differ.</li> <li>• A 3 g dose of fosfomycin trometamol can maintain urinary concentration of &gt;128 mg/L in urine for 24-36 h.</li> <li>• Fraction recovered in urine (48 h): 32-43 %</li> </ul>			
References	<ul style="list-style-type: none"> <li>• Pattel SS <i>et al. Drugs</i>, 1997; 53:637-56</li> <li>• Mazzei T <i>et al. Int J Antimicrob Agents</i> 2006; 28 Suppl 1:S35-41.</li> <li>• Kahlmeter G <i>et al J Antimicrob Chemother</i> 2003; 52:1005-10.</li> <li>• Bergogne-Berezin E. In <i>Antimicrobial Agents</i>. Bryskier S (ed). 2005: p. 972-982</li> </ul>			

## 5. Pharmacodynamics

	Enterobacteriaceae			
fAUC/MIC for bacteriostasis	25 (serum) 3994 (urine)			
fAUC/MIC for 2 log reduction				
fAUC/MIC from clinical data				
Comments				
References	Patel SS et al. <i>Drugs</i> 1997; 53: 637–56 Bergogne-Berezin E. <i>Antimicrobial Agents</i> . Bryskier S (ed). 2005: p. 972-982			

## 6. Monte Carlo simulations and PK/PD breakpoints

Not available.

## 7. Clinical data

Single dose treatment 3 g with fosfomycin trometamol in uncomplicated UTI has been shown to be as effective as trimethoprim (200 mg t.i.d, 5 days), nitrofurantoin (100 mg t.i.d., 7 days), cephalexin (500 mg q.i.d., 5 days), norfloxacin (400 mg b.i.d., 7 days), ofloxacin 200 mg and co-trimoxazole 1.92 g (Naber and Thyroff-Friesinger. *Infection* 1990: Suppl 2: S70-S76).

## 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. For Enterobacteriaceae, breakpoints are S $\leq$ 32 mg/L / R >32 mg/L.
Species without breakpoints	<i>Pseudomonas</i> , <i>Acinetobacter</i> , <i>Staphylococcus</i> , <i>Enterococci</i> , <i>Streptococcus</i> , <i>Neisseria</i> and anaerobes.
Clinical qualifications	Breakpoints apply only to uncomplicated urinary tract infections caused by Enterobacteriaceae.
Dosage	Breakpoints apply to a single oral dose of 3g.
Additional comment	In vitro susceptibility testing with fosfomycin requires the addition of glucose-6-phosphate either to the medium or to the disk or gradient strip. For agar or broth microdilution MIC determination the medium should be supplemented with 25 mg/L of glucose-6-phosphate. In addition to fosfomycin, disks for diffusion susceptibility testing should contain 50 $\mu$ g of glucose-6-phosphate and gradient MIC strips should contain 25 $\mu$ g of glucose-6-phosphate.

## 9. Fosfomycin trometamol - EUCAST clinical MIC breakpoints

These can be found at <http://www.eucast.org>

## 10. Exceptions noted for individual national committees

None.