



# EUCAST

EUROPEAN COMMITTEE  
ON ANTIMICROBIAL  
SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

**Fusidic acid**

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

14<sup>th</sup> April 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. Fusidic acid: Rationale for the clinical breakpoints, version 1.0, 2010. <http://www.eucast.org>.

## Introduction

Fusidic acid has a steroid-like structure but has no hormonal or anti-inflammatory activity. It is the only commercially active agent in the fusidane class. Fusidic acid is active against Gram-positive organisms, particularly staphylococci, and Gram-negative cocci.

Fusidic acid is bactericidal but higher concentrations are required to kill many MRSA. It inhibits protein synthesis by binding to elongation factor G (EF-G) and preventing translation. Resistance is now not uncommon and may be mediated by plasmid mediated mechanisms (*fusB*, *fusC*, *fusD*), chromosomal modification of the EF-G gene, *fusA* or riboprotein modifications. Resistance may be selected readily in vitro and monotherapy is associated with the emergence of resistance. Fusidic acid is commonly used in combination with other agents to prevent the emergence of resistance.

Fusidic acid is especially relevant for staphylococcal skin and soft tissue infections, and is used in the treatment of bone and joint infections. It is available for topical, oral and parenteral use.

## 1. Dosage

	<b>BSAC</b>	<b>CA-SFM</b>	<b>CRG</b>	<b>DIN</b>	<b>NWGA</b>	<b>SRGA</b>
Most common dose	500mg x 2-3	500mg x 2-3	500mg x 3	-	250-500 mg x 2-3	500mg x 3 oral
Maximum dose schedule	500mg x 3	500mg x 3	500mg x 3	-	500 mg x 4	500mg x 4 iv
Available formulations	Oral, iv	Oral, iv	Oral	-	oral, iv	Oral, iv

## 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>Clostridium difficile</i>	0	0	0	0	2	11	96	215	301	170	36	0	0	0	0	0	0	5	0	ND
<i>Staphylococcus aureus</i>	0	0	0	101	1195	4250	6309	2264	533	244	349	653	374	175	35	70	30	27	53	0.5
<i>Staphylococcus aureus</i> MRSA	0	0	0	0	5	88	286	67	2	2	4	17	10	5	1	1	2	0	16	0.5
<i>Staphylococcus aureus</i> MSSA	0	0	0	0	3	68	419	100	6	3	7	22	20	15	3	2	0	1	4	0.5
<i>Staphylococcus coagulase negative</i>	0	0	0	3	3	82	202	190	20	5	1	19	53	135	63	5	0	1	16	0.5
<i>Staphylococcus coagulase negative</i> MRSCN	0	0	0	0	5	84	104	30	4	1	4	11	31	77	111	7	1	1	8	0.5
<i>Staphylococcus epidermidis</i>	0	0	0	1	4	124	52	29	0	0	10	39	82	72	79	2	0	133	9	0.5
<i>Staphylococcus epidermidis</i> MSSE	0	0	0	1	1	8	32	5	3	0	1	5	7	8	13	0	0	0	0	0.5
<i>Staphylococcus haemolyticus</i>	0	0	0	0	2	29	3	0	0	1	14	5	13	14	4	0	0	19	0	0.5
<i>Staphylococcus lugdunensis</i>	0	0	0	0	32	52	3	0	0	0	0	6	1	0	0	0	0	0	0	0.5
<i>Streptococcus agalactiae</i>	0	0	0	0	0	0	0	0	1	3	18	88	555	387	13	6	0	0	0	32
<i>Streptococcus pneumoniae</i>	0	0	0	0	3	19	248	427	21	10	4	8	4	2	5	0	0	0	0	1
<i>Streptococcus pyogenes</i>	0	0	0	2	0	0	1	1	4	9	223	1580	897	46	8	0	0	0	0	16

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<sub>≤</sub> R<sub>></sub>

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA	CLSI
<b>General breakpoint</b>			1/1			0.5/0.5	
Enterobacteriaceae							
<i>Pseudomonas</i> spp.							
<i>Acinetobacter</i> spp.							
<i>Staphylococcus</i> spp.	1/1	2/16			0.5/0.5	0.5/0.5	
<i>Streptococcus</i> spp.							
<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)	<b>500 iv</b>	<b>500 oral</b>		
Cmax (mg/L)	21-52	14-33		
Cmin (mg/L)				
Total body clearance (L/h)				
T ½ (h), mean (range)	10-15	9-16		
AUC24h (mg.h/L)		173-238		
Fraction unbound (%)	2-5			
Volume of distribution (L/kg)	0.3-0.46	0.42-0.52		
Comments	<ul style="list-style-type: none"> <li>• Two values or ranges are given where references differ. Cells are left empty when data are not readily available.</li> <li>• Majority metabolised and excreted via the hepatobiliary system.</li> <li>• There is significant variation between individuals.</li> </ul>			
References	<ul style="list-style-type: none"> <li>• Turnidge. Int J Antimicrob Agents 1999; 12 Suppl: S23-S34</li> <li>• Bryskier. In Antimicrobial Agents 2005, 631-41</li> </ul>			

<b>5. Pharmacodynamics</b>				
fAUC/MIC for bacteriostasis				
fAUC/MIC for 2 log reduction				
fAUC/MIC from clinical data				
Comments	<ul style="list-style-type: none"> <li>• Cells are left empty when data are not readily available.</li> </ul>			
References				

## **6. Monte Carlo simulations and Pk/Pd breakpoints**

Not available.

## **7. Clinical data**

Although there are case reports of therapy with fusidic acid, particularly in combination with other agents, there is little recent documented clinical experience with the use of fusidic acid and no contemporary randomised controlled trials to support its use.

## 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. <i>Staphylococcus</i> spp. S ≤1 and R >1 mg/L
Species without breakpoints	Enterobacteriaceae, <i>Pseudomonas aeruginosa</i> , <i>Acinetobacter</i> spp., <i>Enterococcus</i> spp., <i>Streptococcus</i> spp. other than Group A,B,C,G streptococci, <i>Haemophilus influenzae</i> , <i>Moraxella catarrhalis</i> , <i>Neisseria</i> spp. and anaerobes were considered poor targets for fusidic acid therapy and for that reason did not receive breakpoints.  For Group A,B,C,G streptococci there was considered to be insufficient evidence to set breakpoints.
Clinical qualifications	
Dosage	Breakpoints apply to an oral or iv dosage of 500 mg x 2-3.
Additional comment	

## **9. EUCAST clinical MIC breakpoints**

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

## **10. Exceptions noted for individual national committees**

None