



# EUCAST

EUROPEAN COMMITTEE  
ON ANTIMICROBIAL  
SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

**Nitrofurantoin**

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

21st March 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. Nitrofurantoin: Rationale for the clinical breakpoints, version 1.0, 2010. <http://www.eucast.org>.

## Introduction

The nitrofurans are synthetic compounds. Nitrofurantoin is the most widely used antimicrobial nitrofuran.

Following oral administration, nitrofurantoin is very rapidly excreted via the kidney, resulting in very low serum concentrations and high urinary concentrations. Hence it is used for oral therapy of uncomplicated urinary tract infections. It has useful activity against a range of Gram-positive and Gram-negative organisms that may cause uncomplicated urinary tract infections, although susceptibility of Enterobacteriaceae varies among species, *Escherichia coli* being particularly susceptible and *Proteus* spp. resistant. *Pseudomonas* spp. are resistant.

The antimicrobial activity of nitrofurantoin requires the action of intracellular nitrofuran reductase enzymes. Nitrofurantoin resistance is uncommon and is associated with reduced activity of nitrofuran reductase enzymes.

## 1. Dosage

	<b>BSAC</b>	<b>CA-SFM</b>	<b>CRG</b>	<b>DIN</b>	<b>NWGA</b>	<b>SRGA</b>
Most common dose	50mg x 4	50 mg x 3	50mg x 4	100mg x 2	50 mg x 3-4	50mg x 3
Maximum dose schedule	100mg x 4	50 mg x 6	100mg x 4	100mg x 4	50 mg x 3-4	50mg x 3
Available formulations	Oral	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>Enterococcus faecalis</i>	0	0	0	0	0	0	0	0	0	0	0	1	129	119	5	6	1	0	0	64
<i>Enterococcus faecium</i>	0	0	0	0	0	0	0	0	0	0	0	1	15	40	330	731	776	263	0	256
<i>Escherichia coli</i>	0	0	0	0	0	0	0	0	0	1	14	148	1293	2013	317	96	17	3	0	64
<i>Klebsiella oxytoca</i>	0	0	0	0	0	0	0	0	0	0	0	2	8	14	5	1	0	0	0	ND
<i>Klebsiella pneumoniae</i>	0	0	0	0	0	0	0	0	0	1	1	4	13	14	14	14	9	3	2	ND
<i>Klebsiella spp</i>	0	0	0	0	0	0	0	0	0	0	3	26	99	54	25	10	3	1	0	ND
<i>Staphylococcus aureus</i>	0	0	0	0	0	0	0	0	0	2	9	35	734	786	34	0	0	0	0	32
<i>Staphylococcus epidermidis</i>	0	0	0	0	0	0	0	0	0	0	0	0	1	127	3	0	0	0	0	ND
<i>Staphylococcus saprophyticus</i>	0	0	0	0	0	0	0	0	0	0	0	3	40	28	0	0	0	0	0	ND
<i>Streptococcus agalactiae</i> (group B)	0	0	0	0	0	0	0	0	0	0	3	31	10	2	0	0	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 (IE) no epidemiological cut-off has been determined.

### 3. Breakpoints prior to harmonisation (mg/L) S ≤ R >

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA	CLSI
<b>General breakpoint</b>							
			32/32	64/256			
<b>Species specific breakpoints:</b>							
Enterobacteriaceae	32/32	32/128			32/32	32/32	32/64
<i>Pseudomonas</i> spp.							
<i>Acinetobacter</i> spp.							
<i>Staphylococcus</i> spp.	32/32				32/32	32/32	32/64
<i>Streptococcus</i> spp.	32/32						
<i>Streptococcus pneumoniae</i>							
<i>Enterococcus</i> spp.	32/32	32/128			32/32	32/32	32/64
<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>100 mg</b>			
Cmax (mg/L)	<2 after 1-4 h			
Cmin (mg/L)				
Total body clearance (L/h)				
T ½ (h), mean (range)	0.5-1			
AUC24h (mg.h/L)				
Fraction unbound (%)	25-50			
Volume of distribution (L/kg)	0.6			
Comments	<ul style="list-style-type: none"> <li>• Two values are given where references differ. Cells are left empty when data are not readily available.</li> <li>• Oral absorption &gt;95 %</li> <li>• Concentration in urine &gt;100 mg/L</li> </ul>			
References	<ul style="list-style-type: none"> <li>• Mazzei et al Int J Ant Agents 2006; 28 suppl 1: 35-46.</li> <li>• Finch R. In Antibiotic and Chemotherapy 1997. Churchill-Livingstone; 396-8.</li> </ul>			

## 5. Pharmacodynamics

fAUC/MIC for bacteriostasis				
fAUC/MIC for 2 log reduction				
fAUC/MIC from clinical data				
Comments	<ul style="list-style-type: none"><li>• Pharmacodynamic parameters for nitrofurantoin have not been determined.</li><li>• Cells are left empty when data are not readily available.</li></ul>			
References				

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

No data.

## 7. Clinical data

Clinical trials have shown the efficacy of nitrofurantoin treatment of patients with uncomplicated urinary tract infections caused by bacteria categorized as wild type (e.g. Finh, S. *N Eng J Med* 2003; 349: 259-66). Infections with Enterobacteriaceae other than *E. coli* and staphylococci other than *Staphylococcus saprophyticus* are commonly associated with upper urinary tract or complicated infection.

## 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 <i>E. coli</i> , <i>S. saprophyticus</i> , <i>Enterococcus</i> spp. and streptococcus Group B the breakpoints are 64/64 mg/L.
Species without breakpoints	Enterobacteriaceae other than <i>E. coli</i> , <i>Pseudomonas aeruginosa</i> , <i>Acinetobacter</i> spp., staphylococci other than <i>S. saprophyticus</i> , streptococci other than Group B, <i>Haemophilus influenzae</i> , <i>Moraxella catarrhalis</i> , <i>Neisseria</i> spp. and anaerobes were considered poor targets or inappropriate for nitrofurantoin therapy and for that reason did not receive breakpoints.
Clinical qualifications	Nitrofurantoin is used only for treatment of uncomplicated urinary tract infections.
Dosage	Breakpoints apply to a daily oral dose of 50 mg x 3-4.
Additional comment	

## 9. Nitrofurantoin - EUCAST clinical MIC breakpoints

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

## 10. Exceptions noted for individual national committees

None