

## Moxifloxacin: Rationale for EUCAST Clinical Breakpoints

<b>Current version</b>	<b>3.0</b>	<b>1 January 2021</b>
Previous version	2.3	22 August 2007

### 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.

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. Delafloxacin Rationale Document, version 3.0, 2021. <http://www.eucast.org/rd>."

## Introduction

The fluoroquinolones comprise a class of agents derived from nalidixic acid and developed since the 1960s. The early fluoroquinolones had a limited spectrum of antibacterial activity, mainly against gram-negative pathogens. The newer fluoroquinolone agents have enhanced intrinsic activity against gram-positive organisms and anaerobes and improved pharmacokinetic characteristics in comparison with preceding derivatives. Emergence of resistance is mainly due to mutations in the QRDR region where phenotypic resistance arises as a result of stepwise mutations. Microorganisms with one mutation may exhibit elevated fluoroquinolone MICs that are sometimes difficult to distinguish from wild-type MIC distributions. Other low-level resistance mechanisms include increased activity of efflux pumps, Qnr proteins (capable of protecting DNA gyrase from quinolones) and inactivating enzymes.

EUCAST has defined clinical breakpoints for the fluoroquinolones ciprofloxacin (CIP), levofloxacin (LEV), moxifloxacin (MOX), norfloxacin (NOR) and ofloxacin (OFL). They are with few exceptions available in all European countries. Older fluoroquinolones which are available only in few countries or in topical preparations have not been addressed.

Some fluoroquinolones are available for both oral and intravenous therapy while others are available for oral therapy only. This is reflected in the breakpoints.

Moxifloxacin is used to treat acute exacerbations of chronic bronchitis, community-acquired pneumonia and acute sinusitis. It is more active than ciprofloxacin against streptococci including *Streptococcus pneumoniae* but is less active against *Pseudomonas*.

Moxifloxacin breakpoints underwent revision in 2016.

## 1. Dosage

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose	0.4 g x 1 oral	0.4 g x 1 oral		0.4 g x 1 oral 0.4 g x 1 iv		0.4 g x 1 oral
Maximum dose schedule	0.4 g x 1 oral	0.4 g x 1 oral		0.4 g x 1 oral 0.4 g x 1 iv		0.4 g x 1 oral
Available formulations	oral	oral		oral, iv		oral

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

MIC distributions and ECOFFs can be found at <https://mic.eucast.org/Eucast2/SearchController/search.jsp?action=init>

## 3. Breakpoints prior to harmonisation (mg/L)

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA	CLSI <sup>1</sup>
<b>General breakpoints</b>	ND	1/2		1/2		1/2	
<b>Species related breakpoints</b>							
<i>Enterobacterales</i>	1/1					excluded	
<i>Pseudomonas</i> spp.	1/4					excluded	
<i>Acinetobacter</i> spp.	1/1					excluded	
<i>Staphylococcus</i> spp.	1/2					0.25/0.5	
<i>Streptococcus</i> spp.	1/2					1/2	
<i>Streptococcus pneumoniae</i>	1/2					1/2	1/2
<i>Enterococcus</i> spp.	excluded					excluded	
<i>Haemophilus, Moraxella</i> spp.	1/2					0.25/0.5	1/-

Excluded = considered inappropriate to set a breakpoint, <sup>1</sup>CLSI breakpoints converted to European terminology

#### 4. Pharmacokinetics (PK)

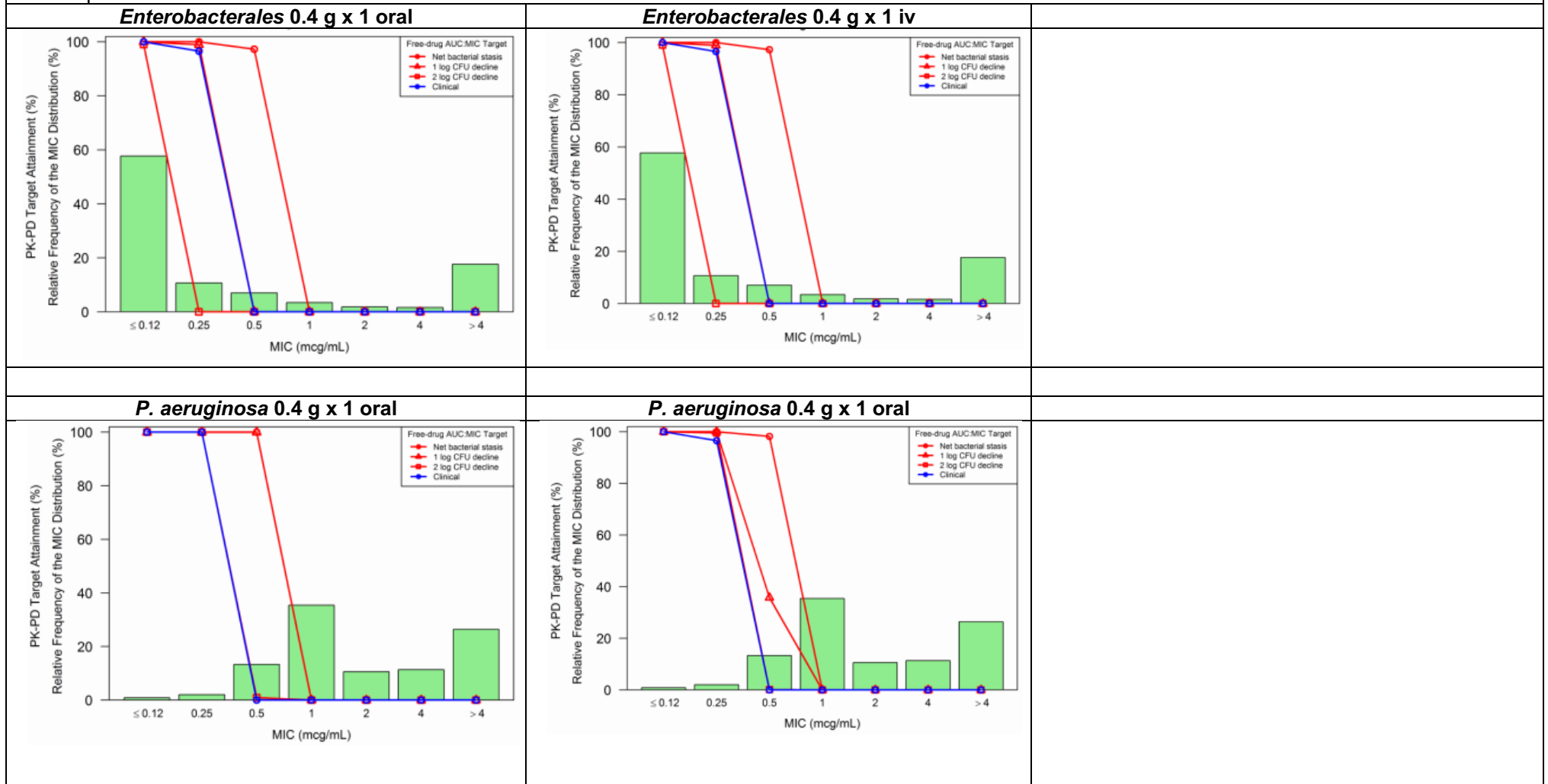
Dosage	0.4 g x 1 iv (Wise)	0.4 g x 1 oral (Wise)	0.4 g x 1 oral/iv (Stass)	0.4 g x 1 iv*	0.4 g x 1 oral*
C <sub>max</sub> (mg/L)	5.1	5.0	2.5/3.6		
C <sub>min</sub> (mg/L)					
Total body clearance (L/h)					
T <sub>1/2</sub> (h), mean (range)	8.2	8.3	15.6 (12.1-19.1) 15.4 (11.6-21.5)		
AUC <sub>0-12</sub> (mg.h/L)					
AUC <sub>0-24</sub> (mg.h/L)	45.3	45.5	29.8 / 34.6	38 (CV 12.4%)	48 (CV 5.6%)
AUC <sub>0-∞</sub> (mg.h/L)					
Fraction unbound (%)			60		60 (50-70)
Volume of distribution <sub>ss</sub> (L)			3.08 / 2.05 (L/kg)		
Comments					
References	<ul style="list-style-type: none"> <li>• Wise R et al., Antimicrob. Agents Chemother. 1999; 43: 1508</li> <li>• Stass H et al. J Antimicrob Chemother 1998; 43 Suppl.B: 83</li> <li>• *USCAST. Quinolone In Vitro Susceptibility Test Interpretive Criteria Evaluations, October 2018 (<a href="https://app.box.com/s/e14zs4u4tpxs02ppjb97czmckvbm99sq">https://app.box.com/s/e14zs4u4tpxs02ppjb97czmckvbm99sq</a>)</li> </ul>				

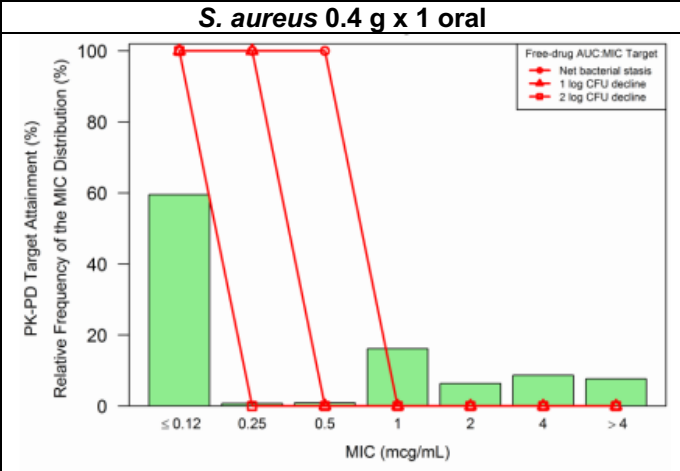
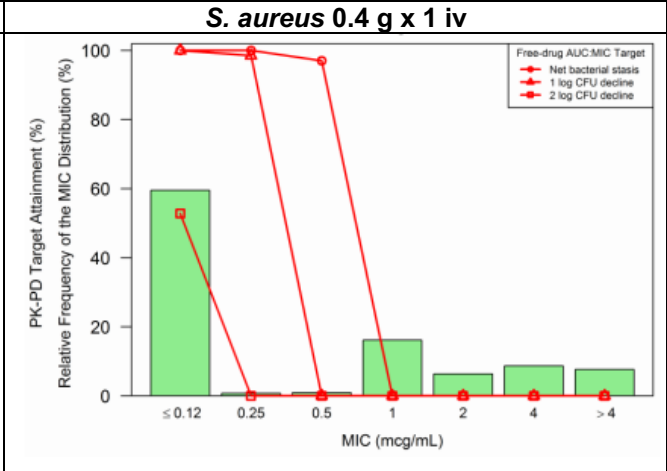
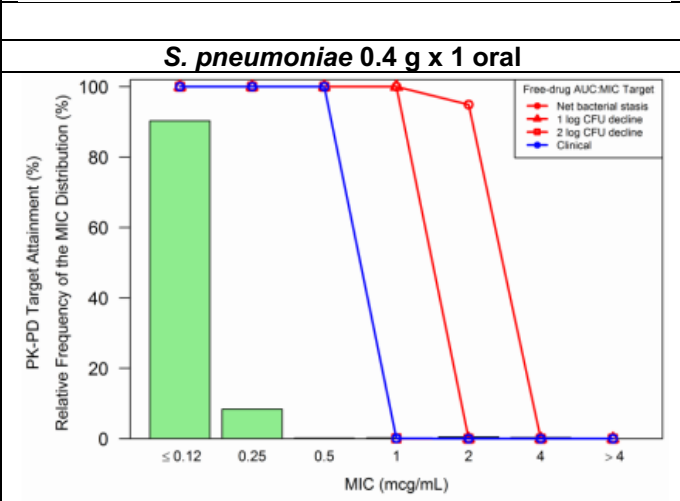
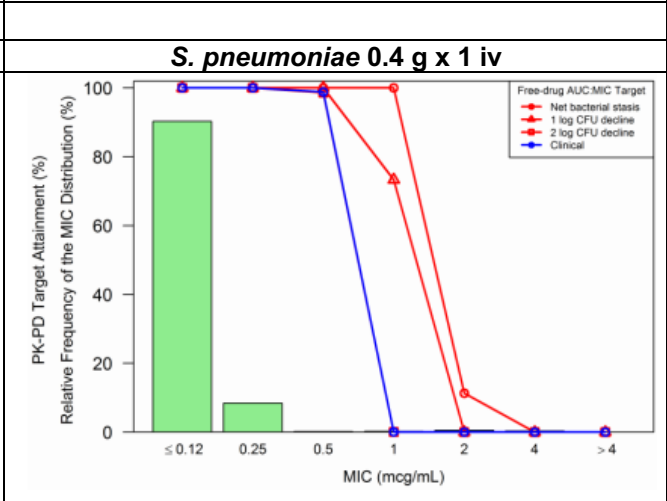
## 5. Pharmacodynamics (PD)

Index	Neutropenic Mouse Thigh						
	<i>Enterobacterales</i> (n=9)	<i>P. aeruginosa</i> (n=3)	<i>S. aureus</i> (n=7)	<i>S. pneumoniae</i> (n=5)			
<i>f</i> AUC/MIC for bacteriostasis	35.6	34.8	35.8	13.1			
<i>f</i> AUC/MIC for 1-log <sub>10</sub> reduction	67.4	47.3	68.7	21.0			
<i>f</i> AUC/MIC for 2-log <sub>10</sub> reduction	140	65.4	187	34.2			
Clinical <i>f</i> AUC/MIC for efficacy	72		-	33.8			
Comments	The clinical <i>f</i> AUC:MIC ratio of 72 (average <i>f</i> AUC:MIC ratio targets for efficacy of 87.5 and 61 for cirpofloxacin and levofloxacin, respectively) was used for <i>Enterobacterales</i> and <i>P.aeruginosa</i> .						
References	<ul style="list-style-type: none"> <li>USCAST. Quinolone In Vitro Susceptibility Test Interpretive Criteria Evaluations, October 2018 (<a href="https://app.box.com/s/e14zs4u4tpxs02ppjb97czmckvbm99sg">https://app.box.com/s/e14zs4u4tpxs02ppjb97czmckvbm99sg</a>)</li> </ul>						

## 6. Monte Carlo simulations

Monte Carlo simulations were conducted by USCAST using PK in healthy subjects with a mean AUC (%CV) of 48 (5.6) for 400 mg x 1oral and 38 (12.4) for 400 mg x1 IV and PD parameters listed in Sections 4 and 5.



<p><b><i>S. aureus</i> 0.4 g x 1 oral</b></p> 	<p><b><i>S. aureus</i> 0.4 g x 1 iv</b></p> 	
<p><b><i>S. pneumoniae</i> 0.4 g x 1 oral</b></p> 	<p><b><i>S. pneumoniae</i> 0.4 g x 1 iv</b></p> 	
<p><b>References</b></p> <ul style="list-style-type: none"> <li>USCAST. Quinolone In Vitro Susceptibility Test Interpretive Criteria Evaluations, October 2018 (<a href="https://app.box.com/s/e14zs4u4tpxs02ppjb97czmckvbm99sg">https://app.box.com/s/e14zs4u4tpxs02ppjb97czmckvbm99sg</a>)</li> </ul>		

## 7. Clinical data

Extensive clinical data are available showing the relationship between exposure (AUC/MIC) and effect of quinolones, in particular for pneumococci. These data are summarized in section 5.

### References

- USCAST. Quinolone In Vitro Susceptibility Test Interpretive Criteria Evaluations, October 2018 (<https://app.box.com/s/e14zs4u4tpxs02ppjb97czmckvbm99sg>)

## 8. Clinical breakpoints (<http://www.eucast.org>)

PK/PD breakpoints (non-species related)	<p>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.</p> <p>S ≤0.25 mg/L    R &gt;0.25 mg/L</p>																					
Species-related breakpoints	<table border="0"> <tr> <td><i>Enterobacterales</i></td> <td>S ≤0.25 mg/L</td> <td>R &gt;0.25 mg/L</td> </tr> <tr> <td><i>Staphylococcus</i> spp.</td> <td>S ≤0.25 mg/L</td> <td>R &gt;0.25 mg/L</td> </tr> <tr> <td><i>Streptococcus</i> A B C G</td> <td>S ≤0.5 mg/L</td> <td>R &gt;0.5 mg/L</td> </tr> <tr> <td><i>S. pneumoniae</i></td> <td>S ≤0.5 mg/L</td> <td>R &gt;0.5 mg/L</td> </tr> <tr> <td><i>H. influenzae</i></td> <td>S ≤0.125 mg/L</td> <td>R &gt;0.125 mg/L</td> </tr> <tr> <td><i>M. catarrhalis</i></td> <td>S ≤0.25 mg/L</td> <td>R &gt;0.25 mg/L</td> </tr> <tr> <td><i>Corynebacterium</i> spp. (not <i>diphtheriae</i>)</td> <td>S ≤0.5 mg/L</td> <td>R &gt;0.5 mg/L</td> </tr> </table>	<i>Enterobacterales</i>	S ≤0.25 mg/L	R >0.25 mg/L	<i>Staphylococcus</i> spp.	S ≤0.25 mg/L	R >0.25 mg/L	<i>Streptococcus</i> A B C G	S ≤0.5 mg/L	R >0.5 mg/L	<i>S. pneumoniae</i>	S ≤0.5 mg/L	R >0.5 mg/L	<i>H. influenzae</i>	S ≤0.125 mg/L	R >0.125 mg/L	<i>M. catarrhalis</i>	S ≤0.25 mg/L	R >0.25 mg/L	<i>Corynebacterium</i> spp. (not <i>diphtheriae</i> )	S ≤0.5 mg/L	R >0.5 mg/L
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Species without breakpoints	<p>The following are considered poor targets for moxifloxacin:</p> <ul style="list-style-type: none"> <li>• <i>Pseudomonas</i> spp.</li> <li>• <i>Acinetobacter</i> spp.</li> </ul> <p>There are no clinical breakpoints for <i>Enterococcus</i> spp. and moxifloxacin, but moxifloxacin has been used for oral step-down treatment of endocarditis caused by <i>Enterococcus</i> spp. The norfloxacin disk diffusion test or the moxifloxacin MIC ECOFF (1 mg/L) can be used to screen for resistance mechanisms. When screen negative, the isolate should be reported “wild type” or “devoid of fluoroquinolone resistance mechanisms”, but not as susceptible to moxifloxacin.</p> <p>There are no clinical breakpoints for viridans group streptococci and moxifloxacin, but moxifloxacin has been used for oral step-down treatment of endocarditis caused by viridans group streptococci. The moxifloxacin MIC ECOFF (0.5 mg/L) can be used to screen for resistance mechanisms. When screen negative, the isolate should be reported “wild type” or “devoid of fluoroquinolone resistance mechanisms”, but not as susceptible to moxifloxacin</p> <p>There is insufficient evidence to set breakpoints for:</p> <ul style="list-style-type: none"> <li>• <i>N. gonorrhoeae</i></li> <li>• <i>N. meningitidis</i></li> <li>• Anaerobes, gram-positive and gram-negative</li> </ul>																					

Clinical qualifications	None
Dosage(s) linked to breakpoints	Standard dosage: 0.4 g x 1 iv and oral
Additional comments	None

### 9. Exceptions noted for individual national committees

None