







	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>Streptococcus equinus</i>	0	0	0	0	0	0	0	1	3	2	1	0	0	0	0	0	0	0	0	0	IE
<i>Streptococcus gordonii</i>	0	0	0	0	1	0	0	0	2	6	0	0	0	0	0	0	0	0	0	0	IE
<i>Streptococcus</i> group C	0	0	0	0	0	0	5	37	100	33	2	0	0	0	0	0	0	0	0	0	2
<i>Streptococcus</i> group G	0	0	0	1	1	0	5	112	410	108	17	2	1	0	0	0	0	0	0	0	2
<i>Streptococcus intermedius</i>	0	0	0	0	0	0	0	8	19	30	16	0	0	0	0	0	0	0	0	0	2
<i>Streptococcus milleri</i>	0	0	0	0	1	0	3	8	47	39	3	0	0	0	0	0	0	0	0	0	2
<i>Streptococcus mitis</i>	0	0	0	0	1	1	1	9	38	106	171	82	5	0	0	1	0	0	0	0	4
<i>Streptococcus mutans</i>	0	0	0	0	0	0	0	0	10	9	9	0	0	0	0	0	0	0	0	0	IE
<i>Streptococcus oralis</i>	0	0	0	0	0	0	0	0	0	0	7	19	16	4	1	0	0	0	0	0	IE
<i>Streptococcus parasanguis</i>	0	0	0	0	0	0	0	0	2	7	2	0	0	0	0	0	0	0	0	0	IE
<i>Streptococcus pneumoniae</i>	0	0	8	13	26	31	104	1534	10058	38077	14228	1182	271	70	109	87	10	3	229	2	
<i>Streptococcus pyogenes</i>	0	0	0	2	3	2	30	3091	6223	787	713	65	5	0	5	0	0	0	234	1	
<i>Streptococcus salivarius</i>	0	0	0	0	1	1	0	2	29	41	12	1	0	0	0	0	0	0	0	0	IE
<i>Streptococcus sanguis</i>	0	0	0	0	0	0	1	3	23	65	33	2	0	0	0	0	0	0	0	0	IE
<i>Streptococcus uberis</i>	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	IE
<i>Streptococcus viridans</i> group	0	0	0	0	0	0	2	5	29	30	26	10	4	2	2	1	0	4	0	0	IE

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<sub>≤</sub>/R<sub>></sub>

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA	CLSI <sup>1</sup>
<b>General breakpoints</b>							
		1/2	1/2	1/2	0.125/2	1/2	
<b>Species related breakpoints</b>							
Enterobacteriaceae	1/1				0.12/2	0.12/1	1/2
<i>Pseudomonas</i> spp.	1/4					1/1	1/2
<i>Acinetobacter</i> spp.						1/1	1/2
<i>Staphylococcus</i> spp.	1/1				0.12/2	0.06/2	1/2
<i>Streptococcus</i> spp.	1/1	excluded			0.12/2	0.12/2	excluded
<i>Streptococcus pneumoniae</i>	0.12/2	excluded			0.12/2	0.12/2	excluded
<i>Enterococcus</i> spp.	excluded	excluded			0.12/2	0.12/2	1/2
<i>Haemophilus/Moraxella</i> spp.	1/1				0.12/0.5	0.12/0.25	1/-
Corynebacteria						excluded	
<i>Neisseria meningitidis</i>	1/1				0.06/0.12	0.03/0.25	
<i>Neisseria gonorrhoeae</i>	0.06/-		0.06/1		0.06/0.12	0.06/0.25	0.06/0.5
<i>Pasteurella multocida</i>						0.12/0.25	
Anaerobes, Gram-positive	excluded					excluded	
Anaerobes, Gram-negative	excluded					excluded	
<i>Campylobacter</i> spp.	1/1						
<i>Helicobacter pylori</i>	2/2						
<i>Bacillus anthracis</i>							0.5/-

excluded = considered inappropriate to set a breakpoint

<sup>1</sup>CLSI breakpoints converted to EUCAST terminology

#### 4. Pharmacokinetics

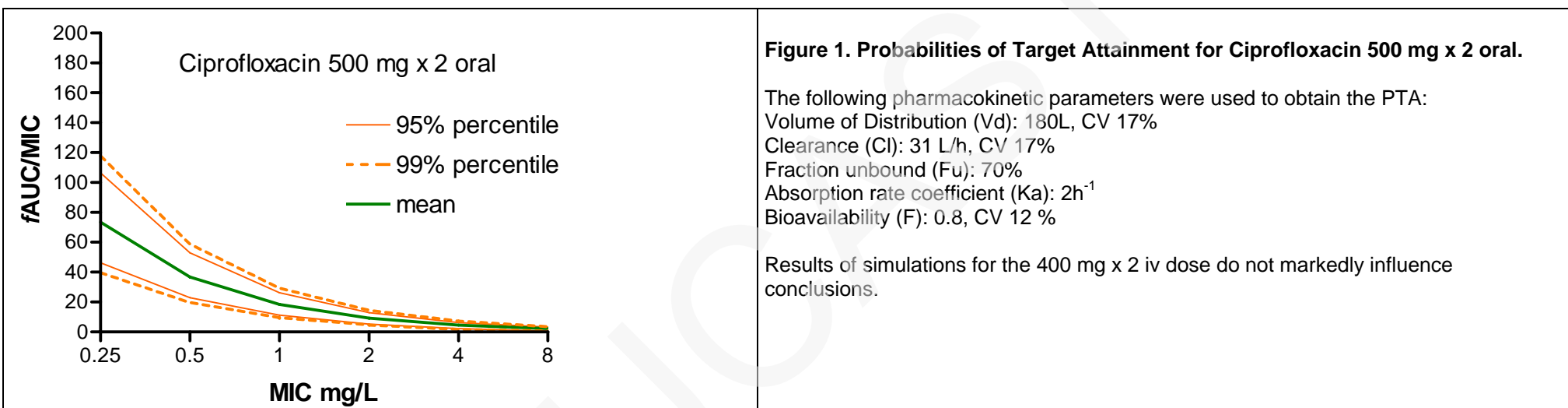
Dosage (mg)	400 x 2 iv	500 x 2 oral	750 x 2 oral	
Cmax (mg/L)	3.2	2.3 - 2.8	3.2 - 3.9	
Cmin (mg/L)				
Total body clearance (L/h)	26.8			
T $\frac{1}{2}$ (h), mean (range)	(4.2 - 4.3)	(2.5 - 3.9)	4.0	
AUC24h (mg.h/L)	21 - 29	19.2 - 19.8	39	
Fraction unbound (%)	70 - 80	70 - 80	70 - 80	
Volume of distribution (L)	100 - 180			
Comments	<ul style="list-style-type: none"> <li>Pharmacokinetic parameters from references Drusano and Dudley were obtained after a 200 mg iv dose; linearity was assumed.</li> <li>AUCs reported for single doses were converted to 24h AUCs assuming linearity.</li> <li>Two values are given where references differ. Cells are left empty when data are not readily available.</li> </ul>			
References	<ul style="list-style-type: none"> <li>Drusano et al., Antimicrob Agents Chemother 1987; 31:860</li> <li>Dudley et al., Antimicrob Agents Chemother 1987; 31:1782</li> <li>Crump et al., Antimicrob Agents Chemother 1983; 24:784</li> <li>Bergan et al., Antimicrob Agents Chemother 1986; 29:298</li> <li>Zlotos et al., J Pharm Sci 1998; 87:215</li> <li>Catchpole et al., J Antimicrob Chemother 1994; 33:103</li> <li>de Marie et al., Int Care Med 1998; 24:343</li> </ul>			

## 5. Pharmacodynamics

	Enterobacteriaceae	<i>Pseudomonas aeruginosa</i>	<i>Streptococcus pneumoniae</i>	<i>Staphylococcus aureus</i>
fAUC/MIC for bacteriostasis	30-40		30 - 40	25-30
fAUC/MIC for 2 log reduction	80-100			60
fAUC/MIC from clinical data	80 – 100	100	30 - 40	
Comments	<ul style="list-style-type: none"> <li>• Data are from non-neutropenic subjects, unless specified otherwise.</li> <li>• Two values are given where references differ. Cells are left empty when data are not readily available.</li> </ul>			
References	<ul style="list-style-type: none"> <li>• Ambrose PG, et al. Infect Dis Clin North Am 2003; 17:529.</li> <li>• Ambrose PG, et al. Antimicrob Agents Chemother 2001; 45:2793.</li> <li>• Forrest A, et al. Antimicrob Agents Chemother 1993; 37: 1073.</li> <li>• Noel AR et al. 47<sup>th</sup> ICAAC, Chicago 2007; Abstract A23.</li> </ul>			

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

Probabilities of Target Attainment (PTA) for 500 mg x 2 oral are shown in Figure 1.



## 7. Clinical data

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

In invasive infections with *Salmonella* spp. there is increasing evidence of clinical failure of ciprofloxacin treatment in cases where there is reduced susceptibility (indicated by resistance to nalidixic acid) due to the acquisition of at least one mutation in *gyrA*.

The risk of ciprofloxacin resistant mutants or of an increase in resistance levels is higher when there is already reduced susceptibility to this antibiotic.

## 8. Clinical breakpoints

Non-species-related breakpoints	<p>Non-species related breakpoints have been determined using Pk/Pd data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints.</p> <p>Breakpoints are <math>S \leq 0.5</math> mg/L, <math>R &gt; 1</math> mg/L. These render wild type Enterobacteriaceae, <i>Pseudomonas</i> spp., <i>Acinetobacter</i> spp., <i>Staphylococcus</i> spp., <i>Haemophilus influenzae</i>, <i>Moraxella catarrhalis</i> and <i>Neisseria</i> spp. susceptible.</p>
Species-related breakpoints	<p>The wild type MIC distributions of most Enterobacteriaceae, including <i>Salmonella</i> spp, exhibit MIC values <math>&lt; 0.125</math> mg/L. A breakpoint of <math>\leq 0.5</math> mg/L allows low-level quinolone resistant Enterobacteriaceae to be categorised as susceptible to ciprofloxacin.</p> <p>For <i>Acinetobacter</i> spp. and <i>Staphylococcus</i> spp. the S/I breakpoint was increased to 1 mg/L to avoid dividing wild type MIC distributions. Therefore these breakpoints relate to the higher dosages of ciprofloxacin.</p> <p>For <i>S. pneumoniae</i>, more than 95% of wild type strains have MICs of 0.25, 0.5 or 1 mg/L, which means that neither of the non-species-related values can be used as a breakpoint without causing major splitting of the wild type distribution and thus problems with the reproducibility of S, I and R categorisation. A breakpoint of <math>S \leq 0.125</math> mg/L categorises wild type <i>S. pneumoniae</i> as intermediate to ciprofloxacin and a breakpoint of <math>R &gt; 2</math> mg/L categorises non-wild type <i>S. pneumoniae</i> as resistant to ciprofloxacin. Both consequences were intended.</p> <p>The breakpoints allow <i>Haemophilus influenzae</i> and <i>Moraxella catarrhalis</i> with low-level fluoroquinolone resistance to be categorized as susceptible to ciprofloxacin.</p> <p>Many laboratories screen for fluoroquinolone resistance with a nalidixic acid 30 µg disc; but note that <i>Neisseria gonorrhoeae</i> and <i>Salmonella typhi</i> that are ciprofloxacin resistant but not clearly nalidixic acid resistant have been reported.</p>
Species without breakpoints	<p><i>Streptococcus</i> spp., <i>Enterococcus</i> spp. and anaerobic bacteria were considered poor targets for ciprofloxacin therapy and for that reason did not receive breakpoints.</p>
Clinical qualifications	<p>There is clinical evidence for ciprofloxacin to indicate a poor response in systemic infections caused by <i>Salmonella</i> spp with low-level fluoroquinolone resistance (<math>MIC &gt; 0.064</math> mg/L). EUCAST has suggested that the epidemiological cut off value (<math>S \leq 0.064/R &gt; 0.064</math> mg/L) be used in <i>Salmonella</i> spp. systemic infections.</p>
Dosage	<p>Breakpoints apply to an oral dose of 500 mg x 2 (or as low as 250 mg x 2 for uncomplicated urinary tract infections) to 750 mg x 2 and an intravenous dose of 400 mg x 2 to 400 mg x 3.</p>
Additional comment	

## 9. Ciprofloxacin - EUCAST clinical MIC breakpoints

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

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<b>10. Exceptions noted for individual national committees</b>
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None
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