

<b>Linezolid</b>	<b>Rationale for the EUCAST clinical breakpoints, version 1.0</b>	<b>18<sup>th</sup> November 2005</b>
------------------	---	--------------------------------------

## Introduction

Linezolid is the only clinically available representative of the oxazolidinones.

Linezolid therapy is relevant for nosocomial pneumonia, community acquired pneumonia, complicated skin- and soft tissue infections caused by staphylococci, streptococci (including *S. pneumoniae*) and enterococci, especially when these organisms are resistant to other appropriate antimicrobials.

Clinical breakpoints have been determined for oral and parenteral (iv) use of linezolid.

## 1. Dosage

	<b>BSAC</b>	<b>CA-SFM</b>	<b>CRG</b>	<b>DIN</b>	<b>NWGA</b>	<b>SRGA</b>	<b>CLSI</b>
<b>Most common dose</b>	600 mg x 2	600 mg x 2	600 mg x 2	600 mg x 2	600 mg x 2	600 mg x 2	600 mg x 2
<b>Maximum dose schedule</b>	NA	N/A	NA	NA	NA	NA	NA
<b>Available formulations</b>	Oral, iv	Oral, iv	oral, iv	Oral, iv	Oral, iv	Oral, iv	Oral, iv

<b>2. Wild type MIC (mg/L) distributions</b>																				
<b>MIC-values:</b>	<b>.002</b>	<b>.004</b>	<b>.008</b>	<b>.016</b>	<b>.032</b>	<b>.064</b>	<b>.125</b>	<b>.25</b>	<b>.5</b>	<b>1</b>	<b>2</b>	<b>4</b>	<b>8</b>	<b>16</b>	<b>32</b>	<b>64</b>	<b>128</b>	<b>256</b>	<b>512</b>	<b>ECOFF*</b>
<i>Enterococcus faecalis</i>	0	0	0	0	0	0	15	36	426	3515	2555	373	6	3	5	0	0	0	0	4
<i>Enterococcus faecium</i>	0	0	0	0	0	0	9	27	362	1548	2101	169	8	0	0	0	0	0	0	4
<i>Haemophilus influenzae</i>	0	0	0	0	0	6	2	7	5	36	121	1478	10796	8927	2732	178	0	0	0	32
<i>Staphylococcus aureus</i>	0	0	0	0	0	9	115	180	1464	18899	36006	3822	28	4	1	0	0	0	0	4
<i>Staphylococcus capitis</i>	0	0	0	0	0	0	5	10	69	170	28	0	0	0	0	0	0	0	0	2
<i>Staphylococcus coagulase neg</i>	0	0	0	0	0	4	8	65	543	3983	1449	110	0	0	0	0	0	0	0	2
<i>Staphylococcus epidermidis</i>	0	0	0	0	0	4	41	375	2066	3717	788	27	1	1	0	0	0	0	0	2
<i>Staphylococcus haemolyticus</i>	0	0	0	0	0	0	2	35	354	662	88	4	1	0	0	0	0	0	0	2
<i>Staphylococcus hominis</i>	0	0	0	0	0	1	1	17	115	490	42	1	0	1	1	0	0	0	0	2
<i>Staphylococcus intermedius</i>	0	0	0	0	0	1	1	0	5	18	5	0	0	0	0	0	0	0	0	ND
<i>Staphylococcus lugdunensis</i>	0	0	0	0	0	0	0	1	16	34	6	0	0	0	0	0	0	0	0	2
<i>Staphylococcus saprophyticus</i>	0	0	0	0	0	0	0	0	7	66	61	8	0	0	0	0	0	0	0	2
<i>Staphylococcus simulans</i>	0	0	0	0	0	0	0	0	7	38	24	0	0	0	0	0	0	0	0	ND
<i>Staphylococcus warnerii</i>	0	0	0	0	0	0	1	0	22	107	17	1	0	0	0	0	0	0	0	2
<i>Staphylococcus xylois</i>	0	0	0	0	0	0	0	0	1	14	7	0	0	0	0	0	0	0	0	ND
<i>Streptococcus agalactiae</i>	0	0	0	0	0	0	0	5	113	1520	208	0	0	0	0	0	0	0	0	2
<i>Streptococcus anginosus</i>	0	0	0	0	0	0	0	1	14	49	12	0	0	0	0	0	0	0	0	ND
<i>Streptococcus bovis</i>	0	0	0	0	0	0	0	1	19	85	25	0	0	0	0	0	0	0	0	2
<i>Streptococcus constellatus</i>	0	0	0	0	0	0	1	5	30	37	1	0	0	0	0	0	0	0	0	ND
<i>Streptococcus group C</i>	0	0	0	0	0	0	3	1	12	123	10	0	0	0	0	0	0	0	0	2
<i>Streptococcus group G</i>	0	0	0	0	0	0	0	0	13	449	68	0	0	0	0	0	0	0	0	2
<i>Streptococcus intermedius</i>	0	0	0	0	0	0	1	0	6	24	8	0	0	0	0	0	0	0	0	ND
<i>Streptococcus milleri</i>	0	0	0	0	0	0	1	3	17	52	2	0	0	0	0	0	0	0	0	ND
<i>Streptococcus mitis</i>	0	0	0	0	0	0	1	3	41	152	4	0	0	0	0	0	0	0	0	2
<i>Streptococcus mutans</i>	0	0	0	0	0	0	0	0	3	9	2	0	0	0	0	0	0	0	0	ND
<i>Streptococcus oralis</i>	0	0	0	0	0	0	0	0	34	81	17	0	1	0	0	0	0	0	0	2
<i>Streptococcus pneumoniae</i>	0	0	0	0	0	10	33	579	4610	38646	15496	18	0	0	0	0	0	0	0	2
<i>Streptococcus pyogenes</i>	0	0	0	0	0	11	252	283	2867	15435	4184	1	1	0	0	0	0	0	0	2
<i>Streptococcus salivarius</i>	0	0	0	0	0	0	1	1	22	41	1	0	0	0	0	0	0	0	0	ND
<i>Streptococcus sanguis</i>	0	0	0	0	0	0	0	1	23	69	3	0	0	0	0	0	0	0	0	ND
<i>Streptococcus viridans</i>	0	0	0	0	0	0	0	0	17	127	60	0	0	0	0	0	0	0	0	2

ECOFF, epidemiological cut-off value as defined by EUCAST; ND, insufficient data for defining epidemiological cut-off value.

**3. Breakpoints prior to harmonisation (mg/L) S<sub>≤</sub> R>**

	<b>BSAC</b>	<b>CA-SFM</b>	<b>CRG</b>	<b>DIN<sup>1</sup></b>	<b>NWGA</b>	<b>SRGA</b>	<b>CLSI</b>
<b>General breakpoints</b>	4 / 4	2/4	4 / 4	-	4 / 4	4 / 4	-
<b>Species related breakpoints</b>							
Staphylococci	4 / 4	2/4			4 / 4	4 / 4	4 / -
Streptococci	4 / 4	2/4				4 / 4	2 / -
<i>S. pneumoniae</i>	4 / 4	2/4			4 / 4	4 / 4	2 / -
Enterococci	4 / 4	2/4			4 / 4	4 / 4	2 / 4
Corynebacteria					IE		
Enterobacteriaceae							
<i>Pseudomonas</i> spp.							
<i>Acinetobacter</i> spp.							
<i>Haemophilus/Moraxella</i> spp.							
<i>N. meningitidis</i>							
<i>N. gonorrhoeae</i>							
<i>P. multocida</i>							
Anaerobes							
<i>Campylobacter</i> spp.							
<i>Helicobacter pylori</i>							

<sup>1</sup> Germany did not have a breakpoint for linezolid prior to the harmonisation process.

<b>4. Pharmacokinetics</b>		
<b>Dosage</b>	<b>600 mg x 2 oral</b>	<b>600 mg x 2 iv</b>
<b>Cmax (mg/L)</b>	15-20	15 - 20
<b>Cmin (mg/L)</b>	6	4
<b>Total body clearance (L/h)</b>	4.5-8.5	4.5-8.5
<b>T<sub>1/2</sub> (h)</b>	4.5-5.5	4.5-5.5
<b>AUC24h (mg.h/L)</b>	200-275	200-275
<b>Fraction unbound (%)</b>	69	69
<b>Volume of distribution (L/kg)</b>	0.7-0.8	0.7-0.8
<b>References</b>	1,2,3	
<b>Comments</b>	Metabolites are inactive and are excreted in urine and through the liver, together with unmetabolised drug. The elimination half life is not influenced by renal function to any extent.	
1. MacGowan,A. JAC 51:Supplement S2: 17, 2003 2. Meagher et al, AAC 47:548, 2003 3. Rayner et al, Clin Pharmacokinetics 42:1411, 2003		

<b>5. Pharmacodynamics</b>			
	<b>Staphylococci<sup>b</sup></b>		
<b>fAUC/MIC for bacteriostasis<sup>a</sup></b>	80		
<b>fAUC/MIC for 2 log drop</b>	-		
<b>fAUC/MIC from clinical data</b>	100		
<b>References</b>	1, 2		
<b>Comments</b>			
<p><sup>a</sup>Linezolid is bacteriostatic against staphylococci, hence a bactericidal AUC/MIC ratio is inappropriate. <sup>b</sup>All available pharmacodynamics are with staphylococci</p> <p>1. MacGowan,A. JAC 51:Supplement S2: 17, 2003 2. Rayner et al, Clin Pharmacokinetics 42:1411, 2003</p>			

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

Linezolid is predominantly bacteriostatic with some persistent antibiotic effects. Studies in animals indicate that the AUC/MIC is the dominant pharmacodynamic index. As linezolid is bacteriostatic against staphylococci, a bactericidal AUC/MIC ratio target is not appropriate. Monte Carlo simulations and target attainment rates for 600mg twice a day linezolid are shown in the table below. Such data support a susceptible breakpoint of  $S_{\leq 1}$  or 2mg/L.

MIC (mg/L)	% target attainment at AUC/MIC target of –		
	50	75	100
0.12	100	100	100
0.25	100	100	100
0.50	100	100	100
1.0	100	100	100
2.0	100	87	83
4.0	75	49	42
8.0	0	0	0

## 7. Clinical data

Randomised controlled clinical trials have shown non-inferiority to established therapies in community acquired pneumonia, hospital acquired pneumonia, and complicated skin and soft tissue infection.

<b>8. Clinical breakpoints</b>	
<b>Non-species-related breakpoints</b>	<p>These have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. The non-species related breakpoint is for use only for species not included in the table.</p> <p>Pharmacodynamic data suggest non-species related breakpoints are <math>S \leq 2</math> mg/L, <math>R &gt; 4</math> mg/L. These render wild type staphylococci, enterococci and streptococci susceptible to linezolid.</p>
<b>Species-related breakpoints</b>	<p>For streptococci, including <i>S. pneumoniae</i>, the breakpoints are <math>S \leq 2</math> mg/L and <math>R &gt; 4</math> mg/L.</p> <p>For staphylococci and enterococci the susceptible breakpoint was increased to <math>\leq 4</math> mg/L to avoid dividing wild type MIC distributions.</p>
<b>Species without breakpoints</b>	Linezolid is not active against Enterobacteriaceae, <i>Pseudomonas</i> spp, <i>Acinetobacter</i> spp, <i>Haemophilus</i> spp, <i>Moraxella</i> spp, <i>Neisseria</i> spp or anaerobic bacteria.
<b>Clinical qualifications</b>	None
<b>Dosage</b>	Breakpoints apply to a linezolid intravenous and oral dosage of 600 mg x 2.
<b>Additional comment</b>	

**9. Exceptions noted for individual national committees**

None

**10. Current EUCAST breakpoints**

The current EUCAST breakpoints are shown on <http://www.eucast.org>