

EUCAST Technical Note on linezolid

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) Steering Committee*

Keywords Breakpoints, EUCAST Technical Note, linezolid, susceptibility testing

Clin Microbiol Infect 2006; 12: 1243–1245

INTRODUCTION

Linezolid is the only member of the oxazolidinones that is available for clinical use. It is a synthetic antibiotic that, depending on the organism and the linezolid concentration, has a bacteriostatic or bactericidal effect by inhibiting protein synthesis. Linezolid is relevant for therapy of nosocomial pneumonia, community-acquired pneumonia and complicated skin and soft-tissue infections caused by staphylococci, streptococci (including *Streptococcus pneumoniae*) and enterococci, especially when these organisms are resistant to other appropriate antimicrobial agents. Linezolid is not active against Enterobacteriaceae, *Pseudomonas* spp., *Acinetobacter* spp., *Haemophilus* spp., *Moraxella* spp., *Neisseria* spp. or anaerobic bacteria, and these organisms have not been allocated breakpoints. Linezolid can be administered orally or intravenously. This Technical Note is based on the linezolid rationale document (available on the EUCAST website: <http://www.eucast.org>). The rationale document includes more details and published references relating to the selection of EUCAST breakpoints.

DOSAGE

Clinical breakpoints have been determined for the oral and intravenous use of linezolid 600 mg twice-daily. No variations in linezolid dosing have been noted among countries.

Corresponding author and reprint requests: G. Kahlmeter, Klinisk mikrobiologi, Centrallasarettet, 351 85 Växjö, Sweden
E-mail: gunnar.kahlmeter@ltkronoberg.se

* G. Kahlmeter (chairman), D. F. J. Brown (scientific secretary), R. Canton (clinical data co-ordinator), A. P. MacGowan (BSAC, UK), J. W. Mouton (CRG, The Netherlands), A. Rodloff (DIN, Germany), F. Goldstein (CA-SFM, France), I. Odenholt (SRGA, Sweden), M. Steinbakk (NWGA, Norway), P. Varaldo (Italy, for EUCAST General Committee), W. Hryniewicz (Poland, for EUCAST General Committee).

MIC DISTRIBUTIONS

The MICs of wild-type *Staphylococcus aureus* and enterococci are ≤ 4 mg/L, and for all coagulase-negative staphylococci and streptococci are ≤ 2 mg/L.

ESTABLISHED BREAKPOINTS

Several of the European breakpoint committees had established breakpoints before the establishment of the EUCAST breakpoints, most commonly, sensitive (S) ≤ 4 /resistant (R) > 4 mg/L, but in some cases S ≤ 2 /R > 4 mg/L.

PHARMACOKINETIC DATA

Based on a standard oral or parenteral dose of 600 mg twice-daily, the pharmacokinetic data used to evaluate linezolid are shown in Table 1. Linezolid has high bioavailability, with similar serum concentrations whether administered orally or intravenously. Metabolites are inactive and are excreted with unmetabolised drug in urine and through the liver. The elimination half-life is not influenced to any extent by renal function.

PHARMACODYNAMIC DATA

Linezolid is predominantly bacteriostatic with some persistent antibiotic effects. Studies in animals indicate that the AUC/MIC is the dominant

Table 1. Pharmacokinetic data for linezolid

Parameter	Data for intravenous administration	Data for oral administration
Dosage	600 mg \times 2 IV	600 mg \times 2 oral
C_{\max} (mg/L)	15–20	15–20
C_{\min} (mg/L)	6	4
Total body clearance (L/h)	4.5–8.5	4.5–8.5
$T_{1/2}$ (h), mean (range)	4.5–5.5	4.5–5.5
AUC _{24 h} (mg.h/L)	200–275	200–275
Fraction unbound (%)	69	69
Volume of distribution (L)	0.7–0.8	0.7–0.8

IV, intravenous.

Table 2. Pharmacodynamic data for linezolid

Pharmacodynamic parameter	Staphylococci
AUC/MIC for bacteriostasis	80
AUC/MIC from clinical data	100

Table 3. Monte Carlo simulation of target attainment for linezolid 600 mg twice-daily

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	100	100	100
2	100	87	83
4	75	49	42
8	0	0	0

pharmacodynamic index. The pharmacodynamic targets for AUC/MIC for staphylococci are shown in Table 2. As linezolid is bacteriostatic against staphylococci, a bactericidal AUC/MIC ratio target is not appropriate. Monte Carlo simulations and target attainment rates for linezolid 600 mg twice-daily are shown in Table 3. Such data support a susceptible breakpoint of $S \leq 1$ or 2 mg/L.

CLINICAL EFFICACY

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

BREAKPOINTS

Breakpoints are summarised in Table 4.

Non-species-related breakpoints

Non-species related breakpoints have been determined mainly on the basis of pharmacokinetic/pharmacodynamic data, and are independent of MIC distributions for specific species. These are for use only with species not mentioned in Table 4, and not with those species for which susceptibility testing is not recommended (marked with ‘-’ or ‘IE’ in EUCAST breakpoint tables). The pharmacodynamic data indicate non-species-related breakpoints of $S \leq 2/R > 4$ mg/L.

Table 4. Summary of EUCAST clinical MIC breakpoints for linezolid, 4 April 2004

Species-related breakpoints (S≤/R>)	
Enterobacteriaceae	-
<i>Pseudomonas</i>	-
<i>Acinetobacter</i>	4/4
<i>Staphylococcus</i> ^a	4/4
<i>Enterococcus</i> ^a	4/4
<i>Streptococcus</i> A, B, C, G	2/4
<i>Streptococcus pneumoniae</i>	2/4
<i>Haemophilus influenzae</i> , <i>Moraxella</i>	-
<i>Neisseria gonorrhoeae</i>	-
<i>Neisseria meningitidis</i>	-
Gram-negative anaerobes	-
Non-species-related breakpoints ^b (S≤/R>)	2/4
Linezolid	-

^aThe S/I breakpoint has been increased from 2.0 to 4.0 mg/L to avoid dividing wild-type MIC distributions; hence there is no intermediate category.
^bNon-species-related breakpoints have been determined mainly on the basis of pharmacokinetic/pharmacodynamic data and are independent of MIC distributions for specific species. They are for use only with species that have not been given a species-specific breakpoint, and not with those species for which susceptibility testing is not recommended (marked with ‘-’ or ‘IE’ in the table).
 -, susceptibility testing not recommended, as the species is a poor target for therapy with the drug; IE, there is insufficient evidence that the species in question is a good target for therapy with the drug.

Species-related breakpoints

Breakpoints of $S \leq 2/R > 4$ mg/L render wild-type streptococci susceptible to linezolid. For staphylococci and enterococci, the susceptible breakpoint was increased to ≤ 4 mg/L to avoid dividing the wild-type MIC distributions. Strains with MICs above the resistant breakpoint are rare. The identification and susceptibility tests for any such isolate must be repeated, and if the result is confirmed, the isolate should be sent to a refer-

ence laboratory. Until there is evidence regarding clinical response, such isolates should be reported as resistant.

Species without breakpoints

Enterobacteriaceae, *Pseudomonas* spp., *Acinetobacter* spp., *Haemophilus* spp., *Moraxella* spp., *Neisseria* spp. and anaerobic bacteria were considered poor targets for linezolid therapy, and for that reason were not allocated breakpoints.