

## EUCAST Technical Note on tigecycline

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

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### INTRODUCTION

Tigecycline is an injectable antibacterial agent derived from the tetracyclines and classified by the manufacturer as a glycylcycline. Tigecycline was registered by the European Medicines Agency (EMA) in May 2006 for parenteral use in complicated skin and skin-structure infections (CSSSIs) and complicated intra-abdominal infections (CIAIs) caused by Enterobacteriaceae (except *Proteus* spp., *Morganella* spp. and *Providencia* spp.), staphylococci, streptococci, *Enterococcus faecalis* and *Enterococcus faecium*. Tigecycline is active against microorganisms that have developed resistance to existing tetracyclines. This Technical Note is based on the EUCAST tigecycline 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 parenteral use of tigecycline 100 mg followed by 50 mg every 12 h in CSSSI and CIAI. Tigecycline has not been licensed previously in Europe, so there is no history of differences in dosages among European countries.

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### MIC DISTRIBUTIONS

The tigecycline MIC values for wild-type staphylococci, streptococci, *Ent. faecalis* and *Ent. faecium* are  $\leq 0.5$  mg/L. The corresponding values for *Escherichia coli*, *Klebsiella* spp., *Citrobacter* spp., *Salmonella* spp. and *Shigella* spp. are  $\leq 2$  mg/L; for *Proteus* spp., *Morganella* spp. and *Providencia* spp. they are  $\leq 8$  mg/L; and for *Pseudomonas* spp. they are  $> 2$  mg/L. Many *Acinetobacter* spp. are inhibited by  $\leq 1$  mg/L, but evidence of clinical efficacy is insufficient (for wild-type MIC distributions, see <http://www.eucast.org>). All MIC values were from tests in freshly prepared medium, which is required to avoid loss of activity of tigecycline in broth.

### ESTABLISHED BREAKPOINTS

None of the European breakpoint committees had established breakpoints for tigecycline before the establishment of the EUCAST breakpoint.

### PHARMACOKINETIC DATA

Based on a standard parenteral dose of 100 mg followed by 50 mg every 12 h, the pharmacokinetic data used to evaluate tigecycline are shown in Table 1.

### PHARMACODYNAMIC DATA

The pharmacodynamics of tetracyclines are not fully understood. They are modestly bactericidal with persistent antimicrobial effects. Limited animal data indicate that AUC/MIC is the pharmacodynamic index best related to outcome. Studies in humans indicate a relationship between AUC/MIC and clinical as well as microbiological efficacy. However, these data are not always easy to interpret because of surgical intervention and mixed bacterial infections. The CART breakpoints (AUC/MIC ratios that discriminate between

**Table 1.** Pharmacokinetic data for tigecycline

Parameter	Pharmacological studies		Efficacy studies 50 mg
	100 mg	50 mg	
$C_{max}$ (mg/L)			
30-min infusion	1.45 ± 0.32	0.87 ± 0.23	0.80 ± 0.46
60-min infusion	0.90 ± 0.27	0.63 ± 0.10	0.49 ± 0.28
$C_{min}$ (mg/L)	NA	0.13 ± 0.08	0.16 ± 0.09
Total body clearance (L/h)	21.8 ± 8.9	23.8 ± 7.8	19.9 ± 8.1
$T_{1/2}$ (h)	27.1 ± 14.3	42.4 ± 35.3	NA
AUC <sub>24h</sub> (mg/L.h)	NA	4.70 ± 1.70	5.85 ± 2.48
AUC <sub>∞</sub> (mg/L.h)	5.19 ± 1.86	NA	NA
Fraction unbound (%)	13–29	13–20	NA
Volume of distribution (L)	568 ± 244	639 ± 307	NA

NA, not available.

populations with a good response and those with a poor response) obtained from human trials with CSSSIs and CIAIs were 12.5 and 6.96, respectively. Monte Carlo simulations using these values indicate that pharmacokinetic/pharmacodynamic breakpoints of ≤0.25 mg/L and ≤0.5 mg/L are appropriate for *Staphylococcus aureus* and *Esch. coli*, respectively.

**CLINICAL EFFICACY**

Tigecycline efficacy studies have been performed in CSSSI and CIAI. In the two CSSSI studies, tigecycline showed clinical and microbiological non-inferiority to the comparator agents (vancomycin plus aztreonam), and the most common isolates were *Staph. aureus*, *Streptococcus pyogenes*, *Esch. coli* and *Ent. faecalis*. In two CIAI trials, tigecycline again showed clinical and microbiological non-inferiority to the comparator agent (imipenem), and the most common isolates were *Esch. coli*, *Bacteroides fragilis* group, *Streptococcus anginosus*, *Klebsiella pneumoniae* and *Ent. faecalis*.

**BREAKPOINTS**

Breakpoints are summarised in Table 2.

**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. 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 EUCAST breakpoint tables). Although incomplete, phar-

**Table 2.** Summary of EUCAST clinical MIC breakpoints for tigecycline, 30 March 2006

Species-related breakpoints (S</th>												
Enterobacteriaceae	Pseudomonas	Acinetobacter	Staphylococcus	Enterococcus	Streptococcus A, B, C, G	Streptococcus pneumoniae	Streptococcus pneumoniae	Haemophilus influenzae, Moraxella catarrhalis	Neisseria gonorrhoeae	Neisseria meningitidis	Gram-negative anaerobes	Non-species-related breakpoints* (S</th>
Tigecycline	1/2 <sup>b,c</sup>	-	IE	0.25/0.5 <sup>d,e</sup>	0.25/0.5 <sup>d</sup>	0.25/0.5 <sup>d</sup>	IE	IE	IE	IE	Note <sup>f</sup>	0.25/0.5

\*Non-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).  
<sup>b</sup>Tigecycline has decreased activity against *Morganella*, *Proteus* and *Providencia*.  
<sup>c</sup>The S/I and I/R breakpoints were increased to avoid dividing wild-type distributions of relevant species.  
<sup>d</sup>Strains with MIC values above the S/I breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests for any such isolate must be repeated, and if the result is confirmed, the isolate should be sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MICs above the current resistant breakpoint (in italics), they should be reported as resistant.  
<sup>e</sup>The S/I breakpoint was increased to avoid dividing wild-type distributions of relevant species.  
<sup>f</sup>For anaerobic bacteria, there is clinical evidence of activity in mixed intra-abdominal infections, but no correlation between MIC values, pharmacokinetic/pharmacodynamic data and clinical outcome. Therefore, no breakpoint for susceptibility testing is given.  
 -, Susceptibility testing is not recommended, as the species is a poor target for therapy with tigecycline; IE, there is insufficient evidence that the species in question is a good target for therapy with tigecycline.

macodynamic data suggest non-species-related breakpoints in the region of susceptible (S)  $\leq 0.25$  and resistant (R)  $> 0.5$  mg/L for tigecycline.

### Species-related breakpoints

A susceptible breakpoint of 0.25 mg/L for streptococci and enterococci, and of 0.5 mg/L for staphylococci, would render wild-type staphylococci, streptococci and enterococci susceptible to tigecycline. This would be reasonably compatible with pharmacokinetic, pharmacodynamic and clinical data, and would not split wild-type populations. Resistant isolates are rare or non-existent, and it is recommended that the identification and antimicrobial susceptibility tests are repeated for strains with MIC values above the S/I breakpoint; if the result is confirmed, the isolate should be sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MICs above the current resistant breakpoint, they should be reported as resistant.

There is clinical evidence to suggest that wild-type *Esch. coli*, *Klebsiella* spp. and *Enterobacter* spp. respond to tigecycline therapy. A susceptible breakpoint of 1 mg/L would render wild-type

Enterobacteriaceae (except *Proteus* spp., *Morganella* spp. and *Providencia* spp., which have higher MIC values and a doubtful clinical response) susceptible to tigecycline and largely undivided by the breakpoint.

### Species without breakpoints

For anaerobic bacteria, there is clinical evidence of activity in mixed intra-abdominal infections, but no correlation between MIC values, pharmacokinetic/pharmacodynamic data and clinical outcome. Therefore, no breakpoint for susceptibility testing is given.

For *Acinetobacter* spp., *Haemophilus influenzae*, *Moraxella catarrhalis*, *Neisseria* spp. and *Streptococcus pneumoniae*, the MIC values imply that infections with these organisms might be treated with tigecycline, but the clinical evidence is currently limited and these organisms are not within the approved indications. Tigecycline has reduced activity against *Proteus* spp., *Morganella* spp., *Providencia* spp. and *Pseudomonas* spp. These organisms have not been allocated breakpoints, and laboratories are advised not to test these genera.