

<b>Tigecycline</b>	<b>Rationale for the EUCAST clinical breakpoints, version 1.0</b>	<b>30 March 2006</b>
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## Introduction

Tigecycline is an injectable antibacterial derived from the tetracyclines and classified by the manufacturer as a glycylcycline. Its in vivo potency is similar to tetracyclines with the exception that it is active against bacterial strains which are resistant to existing tetracyclines. It is available only in an intravenous formulation, and has a large volume of distribution. Nausea is the most noteworthy adverse event.

Tigecycline is licenced for use in complicated skin and skin structure infections (CSSSI), and complicated intra-abdominal infection (IAI).

Tigecycline has clinically useful activity against staphylococci,  $\beta$ -haemolytic streptococci, enterococci, *E. coli*, *Klebsiella* spp., and several other Enterobacteriaceae.

EUCAST has determined clinical breakpoints for the use of parenteral (iv) tigecycline.

## 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>							
<b>Maximum dose schedule</b>							
<b>Available formulations<sup>1</sup></b>	Not registered	Not registered	Not registered	Not registered	Not registered	Not registered	Not registered

<sup>1</sup> Not registered at the time breakpoints were assessed. Clinical breakpoints were determined for the parenteral use of tigecycline 100mg followed by 50mg 12 hourly.





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

	BSAC <sup>1</sup>	CA-SFM <sup>1</sup>	CRG <sup>1</sup>	DIN <sup>1</sup>	NWGA <sup>1</sup>	SRGA <sup>1</sup>	CLSI <sup>2</sup>
General breakpoints							
Species related breakpoints							
Staphylococci							
Streptococci							
<i>S. pneumoniae</i>							
Enterococci							
Corynebacteria							
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>							
<i>Campylobacter</i> spp.							
<i>Helicobacter pylori</i>							

<sup>1</sup> None of the European countries had existing breakpoints for tigecycline prior to registration.

<sup>2</sup>The CLSI (USA) has not yet determined breakpoints for tigecycline..

<b>4. Pharmacokinetics</b>				
	Pharmacological studies		Efficacy studies	
<b>Dosage</b>	100mg	50mg	50mg	
<b>C<sub>max</sub> (mg/L) 30 min inf</b>	1.45 ± 0.32	0.87 ± 0.23	0.80 ± 0.46	
<b>60 min inf</b>	0.90 ± 0.27	0.63 ± 0.10	0.49 ± 0.28	
<b>C<sub>min</sub> (mg/L)</b>	NA	0.13 ± 0.08	0.16 ± 0.09	
<b>Total body clearance (L/h)</b>	21.8 ± 8.9	23.8 ± 7.8	19.9 ± 8.1	
<b>T<sub>1/2</sub> (h)</b>	27.1 ± 14.3	42.4 ± 35.3	NA	
<b>AUC<sub>24</sub> (mg/L.h)</b>	NA	4.70 ± 1.70	5.85 ± 2.48	
<b>AUC<sub>∞</sub> (mg/L.h)</b>	5.19 ± 1.86	NA	NA	
<b>Fraction unbound (%)</b>	13-29	13-20	NA	
<b>Volume of distribution (L)</b>	568 ± 244	639 ± 307	NA	
Sun et al., Antimicrob Agents Chemother 2005 49:1629 Meagher et al., Clin Infect Dis 2005 41 suppl5:334 Muralidhan et al., Antimicrob Agents Chemother 2005 49:220 Data on file, Wyeth Inc., USA				

NA, Not available

## 5. Pharmacodynamics

The pharmacodynamics of tetracyclines are not fully understood. Limited animal data indicates that AUC/MIC is the pharmacodynamic index best related to outcome. Human pharmacodynamic studies indicate a relationship between AUC/MIC and clinical as well microbiological efficacy. Figures 1 and 2 show the response curves for the CSSI and CIAI infections, respectively. The CART breakpoints (AUC/MIC ratios that discriminate between populations with a good response versus those with a poor response) obtained from these data were 12.5 and 6.96, respectively.

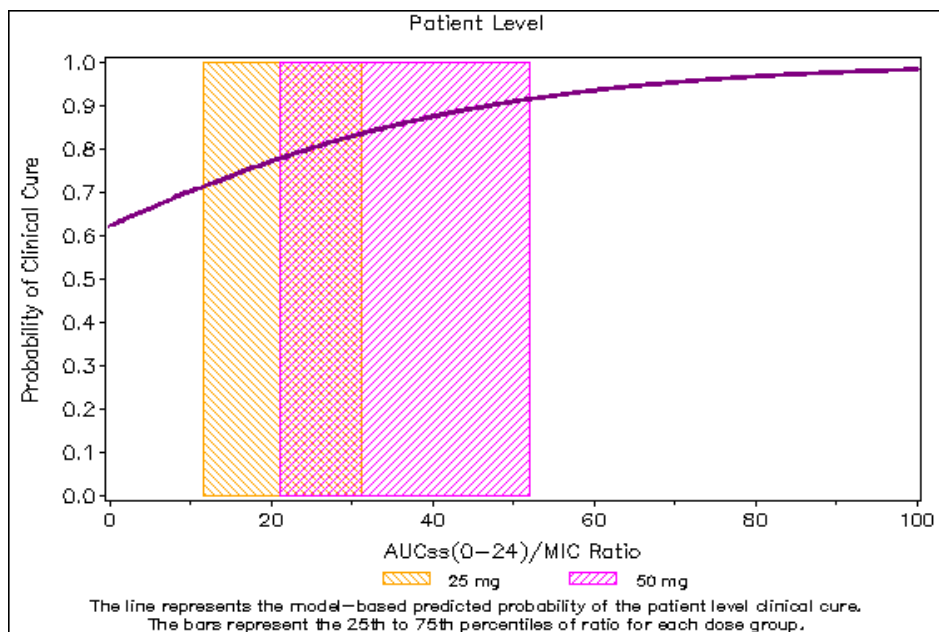


Figure 1. Regression model for cSSI

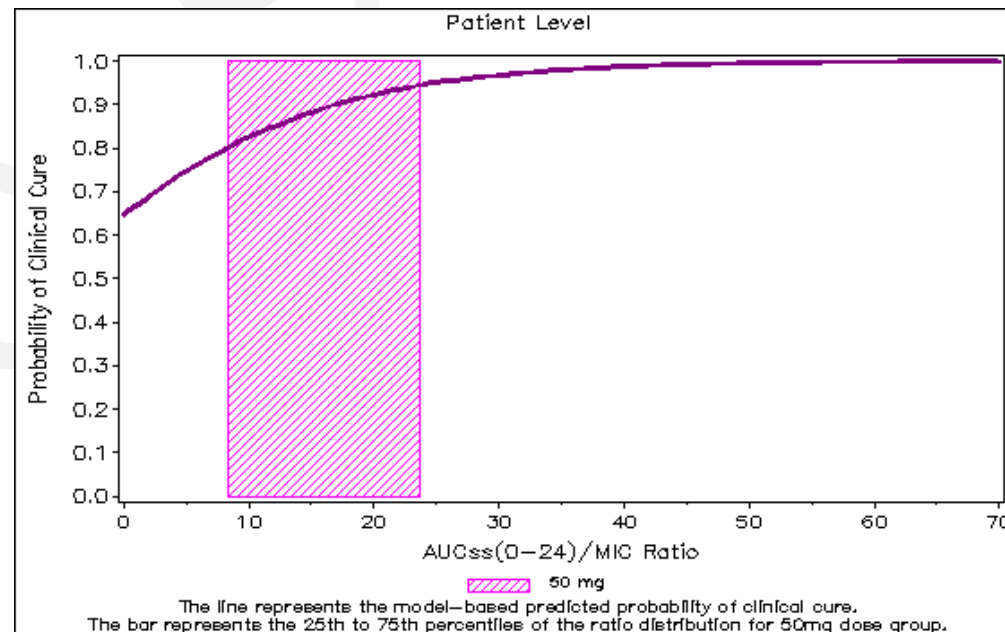
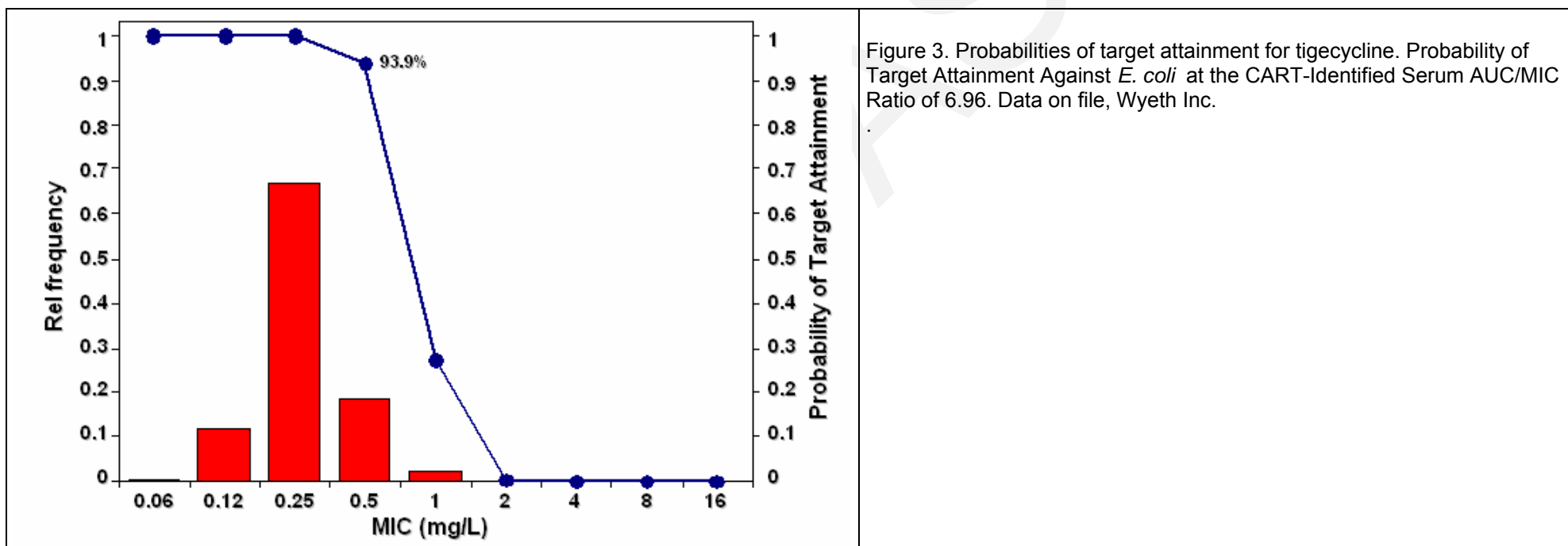


Figure 2. Regression model for CIAI.

References: Meagher et al. 2005 ECCMID poster 1184 , Data on file, Wyeth Inc.

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

Figure 3 shows the probability of target attainment for *E. coli*. The target is taken from the clinical study on and complicated intra-abdominal infection. The use of this target in the Monte Carlo simulations suggests a Pk/Pd breakpoint of  $\leq 0.25$ - $0.5$ mg/L. Similarly, for Gram-positives simulations suggest a Pk/Pd breakpoint of  $\leq 0.25$  mg/L using the target of 12.5 obtained from the clinical cSSSI study (data not shown).



## 7. Clinical data

Tigecycline registration studies have been performed in complicated skin and skin structure infections, and complicated intra-abdominal infections. In the two CSSSI studies, tigecycline showed clinical and microbiological non-inferiority to the comparators (vancomycin plus aztreonam). The most common isolates were *S. aureus*, *S. pyogenes*, *E. coli* and *E. faecalis*. In two CIAI trials, tigecycline showed clinical and microbiological non-inferiority to the comparator (imipenem/cilastatin). The most common isolates were *E. coli*, *B. fragilis* group, *S. anginosus*, *K. pneumoniae* and *E. faecalis*.

<b>8. Clinical breakpoints</b>	
<b>Non-species-related breakpoints</b>	<p>Relationships for tetracyclines are not fully understood but AUC/MIC is a significant factor determining outcome in human trials. There is some discrepancy between simple animal experiments and complex human infections. Mixed organisms are common in human infections and surgical intervention has a significant effect on outcome than the antimicrobial agents in CIAI.</p> <p>On the basis of available Pk/Pd data breakpoints are <math>S \leq 0.25</math> and <math>R &gt; 0.5</math> mg/L.</p>
<b>Species-related breakpoints</b>	<p>Enterobacteriaceae, with the exclusion of <i>Proteus</i>, <i>Morganella</i> and <i>Providencia</i>, <math>S \leq 1</math> and <math>R &gt; 2</math> mg/L.  <i>Staphylococcus</i> spp. <math>S \leq 0.5</math> and <math>R &gt; 0.5</math> mg/L  <i>Streptococcus</i> spp. (except <i>S.pneumoniae</i>) and <i>Enterococcus</i> spp. <math>S \leq 0.25</math> and <math>R &gt; 0.5</math> mg/L.</p> <p>For anaerobic bacteria there is clinical evidence of activity in mixed intra-abdominal infections, but no correlation between MIC values, Pk/Pd data and clinical outcome. Therefore no breakpoint for susceptibility testing is given.</p>
<b>Species without breakpoints</b>	<p>For <i>Acinetobacter</i> spp, <i>H. influenzae</i>, <i>M. catarrhalis</i>, <i>Neisseria</i> spp. and <i>Streptococcus pneumoniae</i> the MIC values imply that infections with these organisms might be treated with tigecycline but the clinical evidence is currently limited and the organisms not within the approved indications.</p> <p>Tigecycline has reduced activity against <i>Proteus</i> spp., <i>Morganella</i> spp., <i>Providencia</i> spp. and <i>Pseudomonas</i> spp. These organisms have not received breakpoints.</p> <p>For anaerobic bacteria there is clinical evidence of activity in mixed intra-abdominal infections, but no correlation between MIC values, Pk/Pd data and clinical outcome. Therefore no breakpoint for susceptibility testing is given.</p>
<b>Clinical qualifications</b>	Breakpoints apply only to CSSSI and CIAI
<b>Dosage</b>	Breakpoints apply to a tigecycline intravenous dose of 100 mg followed by 50mg 12 hourly for CSSSI and CIAI.
<b>Additional comment</b>	None

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

None

**10. Current EUCAST breakpoints**

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