

## Introduction

The glycopeptides are a class of agents composed of amino acid residues and attached sugars. Glycopeptides were first used in the 1950s but were not widely used until the emergence of multi-resistant staphylococci in the 1980s. Glycopeptides are active against Gram-positive bacteria but Gram-negative bacteria are intrinsically resistant. The clinically available glycopeptides differ in potency and pharmacokinetics. Acquired resistance to glycopeptides is most common in enterococci and is based on acquisition of various *van* gene complexes. These genes have rarely been found in *Staphylococcus aureus*. Changes in cell wall structure in *S. aureus* also result in teicoplanin resistance, which is most commonly heterogeneous (formerly referred to as GISA/hGISA isolates). Low-level resistance to teicoplanin is also seen in some coagulase-negative staphylococci, especially in *Staphylococcus haemolyticus*.

EUCAST has defined clinical breakpoints for the parenteral use of the glycopeptides vancomycin and teicoplanin, which are available throughout Europe. Unlike vancomycin, no oral formulation of teicoplanin is available. Since vancomycin and teicoplanin are active against the same microorganisms, the same species or species groups have received breakpoints for both glycopeptides.

Teicoplanin is used to treat severe or complicated infections caused by multi-resistant microorganisms among *Staphylococcus* spp., *Enterococcus* spp. and *Streptococcus* spp. (including *Streptococcus pneumoniae*). In clinical practice, teicoplanin is effective in the therapy of skin and soft tissue infection, pneumonia, urinary infection, prosthetic device associated infection and other systemic infections.

## 1. Dosage

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose (mg)	400 x 1 (with loading dose of 400 mg)	200-400 x 1	200-400 x 1	200-400 x 1	400 x 2	6 mg/kg x 2 for 1d, then 6 mg/kg x 1
Maximum dose schedule (mg)	600 x 2	400 x 2	800 x 1	800 x 1	400 x 2	400 x 2
Available formulations	iv, im	iv, im	iv, im	iv, im	iv, im	iv



	<b>0.002</b>	<b>0.004</b>	<b>0.008</b>	<b>0.016</b>	<b>0.032</b>	<b>0.064</b>	<b>0.125</b>	<b>0.25</b>	<b>0.5</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>Streptococcus pyogenes</i>	0	0	0	12	16	92	267	57	1	0	0	0	0	0	0	0	0	0	0	0	0.5
<i>Streptococcus viridans</i> group	0	0	0	5	26	63	280	129	26	4	0	0	0	0	0	0	0	0	0	0	0.5

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 no epidemiological cut-off has been determined (ND).

<b>3. Breakpoints prior to harmonisation (mg/L) S<sub>≤</sub>/R<sub>&gt;</sub></b>							
	<b>BSAC</b>	<b>CA-SFM</b>	<b>CRG</b>	<b>DIN</b>	<b>NWGA</b>	<b>SRGA</b>	<b>CLSI<sup>1</sup></b>
<b>General breakpoints</b>							
		4/16	4/8	4/16	4/8	4/4	
<b>Species related breakpoints</b>							
Enterobacteriaceae							
<i>Pseudomonas</i> spp.							
<i>Acinetobacter</i> spp.							
<i>Staphylococcus</i> spp.	4/4	4/16			4/8	4 / 4	8/16
<i>Streptococcus</i> spp.	4/4	4/16				0.5/4	
<i>Streptococcus pneumoniae</i>	4/4	4/16			2/4	0.5/4	
<i>Enterococcus</i> spp.	4/4	4/16			4/8	4/4	8/16
<i>Haemophilus</i> spp.							
<i>Moraxella</i> spp.							
Corynebacteria							
<i>Neisseria meningitidis</i>							
<i>Neisseria gonorrhoeae</i>							
<i>Pasteurella multocida</i>							
Anaerobes Gram-positive							
Anaerobes Gram-negative							
<i>Campylobacter</i> spp.							
<i>Helicobacter pylori</i>							
<i>Bacillus anthracis</i>							

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

#### 4. Pharmacokinetics

Dosage	400mg x 1 or 6mg/kg x 1			
Cmax (mg/L)	40-45			
Cmin (mg/L)	<5			
Total body clearance (L/h/kg)	-			
T ½ (h), mean (range)	Multi-phased			
AUC24h (mg.h/L)	550			
Fraction unbound (%)	10			
Volume of distribution (L/kg)	0.9-1.6			
Comment	<ul style="list-style-type: none"><li>• The drug is not absorbed from the intestines, is not metabolised and is excreted through glomerular filtration. The half life of teicoplanin is multi-phased, the terminal half life being very long (360h).</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>• Greenwood, D. Antibiotic and Chemotherapy 2003; 8<sup>th</sup> Edn: 301</li><li>• Van Bambeke F et al. Drugs 2004; 64: 913.</li></ul>			

## 5. Pharmacodynamics

AUC/MIC for bacteriostasis				
AUC/MIC for 2 log reduction				
fAUC/MIC from clinical data				
Comments	<ul style="list-style-type: none"><li>• There are limited clinical data relating pre-dose (trough) teicoplanin concentrations to clinical outcome.</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>• Harding et al. J Antimicrob Chemother 2000; 45: 835.</li></ul>			

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

Insufficient data.

## **7. Clinical data**

Randomised controlled trials performed for registration purposes indicate that teicoplanin has clinical activity against susceptible pathogens in infections including skin and soft tissue, bone and joints, lung, urinary tract infection and those which are associated with prostheses.

There is some evidence that doses greater than those used in clinical trials may be necessary to optimise clinical outcomes in some circumstances.

## 8. Clinical breakpoints

Non-species-related breakpoints	There are insufficient data to set non-species-related breakpoints.
Species-related breakpoints	<p>Breakpoints were based on Pk data, microbiological data and clinical experience.</p> <p>For <i>S. aureus</i> the breakpoints are 2/2 mg/L to avoid reporting “GISA” isolates intermediate, as serious infections with “GISA” isolates are not treatable with increased doses of teicoplanin.</p> <p>For coagulase-negative staphylococci, the breakpoints are 4/ 4mg/L to avoid dividing the wild type MIC distribution.</p> <p>For <i>Enterococcus</i> spp, the breakpoints are 2/2 mg/L to avoid the possibility of reporting <i>vanA</i> isolates intermediate to teicoplanin but resistant to vancomycin.</p> <p>For streptococci, including <i>Streptococcus pneumoniae</i>, and Gram-positive anaerobes breakpoints were set at 2/2 mg/L as strains with MIC values above 2 mg/L are rare or not yet reported.</p>
Species without breakpoints	Enterobacteriaceae, <i>Pseudomonas</i> spp., <i>Acinetobacter</i> spp., <i>Haemophilus influenzae</i> , <i>Moraxella catarrhalis</i> spp., <i>Neisseria</i> spp. and anaerobes are considered poor targets for teicoplanin therapy and for that reason did not receive breakpoints.
Clinical qualifications	
Dosage	Breakpoints apply to an intravenous dose of 400 mg x 1 to 800mg x 1 or 400 mg x 2.
Additional comment	Glycopeptide breakpoints have been revised in the light of concerns regarding reporting of VISA isolates as susceptible, the absence of evidence for successful treatment of infections caused by enterococci appearing intermediate with previous breakpoints, and the few pharmacodynamic data now available.

## 9. Teicoplanin - EUCAST clinical MIC breakpoints

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

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