

Rationale for EUCAST clinical breakpoints

Agent	Tedizolid	
Current version	1.0	19 April 2018
Previous versions		

Foreword

EUCAST

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) is organised by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), the European Centre for Disease Prevention and Control (ECDC), and the active national antimicrobial breakpoint committees in Europe. EUCAST was established by ESCMID in 1997, was restructured in 2001-2002 and has been in operation in its current form since 2002. The current remit of EUCAST is to harmonise clinical breakpoints for existing drugs in Europe, to determine clinical breakpoints for new drugs, to set epidemiological (microbiological) breakpoints, to revise breakpoints as required, to harmonise methodology for antimicrobial susceptibility testing, to develop a website with MIC and zone diameter distributions of antimicrobial agents for a wide range of organisms and to liaise with European governmental agencies and European networks involved with antimicrobial resistance and resistance surveillance.

Information on EUCAST and EUCAST breakpoints is available on the EUCAST website at <http://www.EUCAST.org>.

EUCAST rationale documents

EUCAST rationale documents summarise the information on which the EUCAST clinical breakpoints are based.

Availability of EUCAST documents

All EUCAST documents are freely available from the EUCAST website at <http://www.EUCAST.org>.

Citation of EUCAST documents

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This rationale document should be cited as: "European Committee on Antimicrobial Susceptibility Testing. Tedizolid: Rationale for the clinical breakpoints, version 1.0 2017. <http://www.eucast.org>."

1. Introduction

Tedizolid belongs to the oxazolidinone class of antibacterial agents. Tedizolid phosphate is a prodrug that is converted by phosphatases to tedizolid, the microbiologically active moiety, following oral and intravenous (i.v.) administration. The antibacterial activity of tedizolid occurs through inhibition of bacterial protein synthesis by binding to 23S ribosomal RNA (rRNA) of the 50S subunit of the bacterial ribosome.

In vitro time-kill studies show that tedizolid has bacteriostatic activity against staphylococci, streptococci, and enterococci. In a limited number of *Staphylococcus aureus* strains tested, the presence of the chloramphenicol-florfenicol resistance (*cfr*) gene did not result in resistance to tedizolid in the absence of chromosomal mutations. Organisms resistant to oxazolidinones via mutations in chromosomal genes encoding 23S rRNA or ribosomal proteins (L3 and L4) are generally cross-resistant to linezolid. Spontaneous mutations conferring reduced susceptibility to tedizolid occur *in vitro* at a frequency rate of approximately 10^{-10} .

Tedizolid is licensed for use in adults for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by isolates of Gram-positive bacteria designated susceptible to tedizolid.

2. Dosage

Standard dose schedule	Oral or iv: 200 mg once daily for 6 days
Maximum dose schedule	Oral or iv: 200 mg once daily for 6 days
Available formulations	Oral 200 mg tablets, iv 200 mg powder

3. MIC distributions and epidemiological cut-off (ECOFF) values (mg/L)

	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
<i>Staphylococcus aureus</i>	0	0	0	4	2	11	539	4754	2450	15	4	5	2	1	0	0	0	0	0	
<i>Staphylococcus aureus</i> MRSA	0	0	0	2	0	7	264	2028	922	11	3	5	1	1	0	0	0	0	0	
<i>Staphylococcus aureus</i> MSSA	0	0	0	2	2	4	275	2726	1528	4	1	0	1	0	0	0	0	0	0	
<i>Staphylococcus haemolyticus</i>	0	0	0	0	0	0	27	122	5	1	0	0	0	0	0	0	0	0	0	
<i>Staphylococcus lugdunensis</i>	0	0	0	0	0	0	68	74	3	0	0	0	0	0	0	0	0	0	0	
<i>Streptococcus pyogenes</i>	0	0	0	2	1	21	386	301	1	0	0	0	0	0	0	0	0	0	0	
<i>Streptococcus agalactiae</i>	0	0	0	1	0	3	238	459	7	0	0	0	0	0	0	0	0	0	0	
<i>Streptococcus anginosus</i> group	0	0	0	11	11	13	40	16	0	0	0	0	0	0	0	0	0	0	0	
<i>Streptococcus</i> groups C, F, G	0	0	0	0	1	4	23	17	0	0	0	0	0	0	0	0	0	0	0	
<i>Streptococcus viridans</i> group	0	0	0	0	0	2	6	29	2	0	0	0	0	0	0	0	0	0	0	
<i>Enterococcus faecalis</i>	0	0	0	4	0	3	33	430	345	5	1	0	1	0	0	0	0	0	0	
<i>Enterococcus faecium</i>	0	0	0	0	1	0	23	190	172	8	2	1	0	0	0	0	0	0	0	
<i>Peptostreptococcus</i> spp.	0	0	0	2	4	3	7	3	2	6	3	1	0	0	0	0	0	0	0	

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. Some combined distributions may include distributions truncated at concentrations below 512 mg/L. When there is insufficient evidence no epidemiological cut-off has been determined (ND).

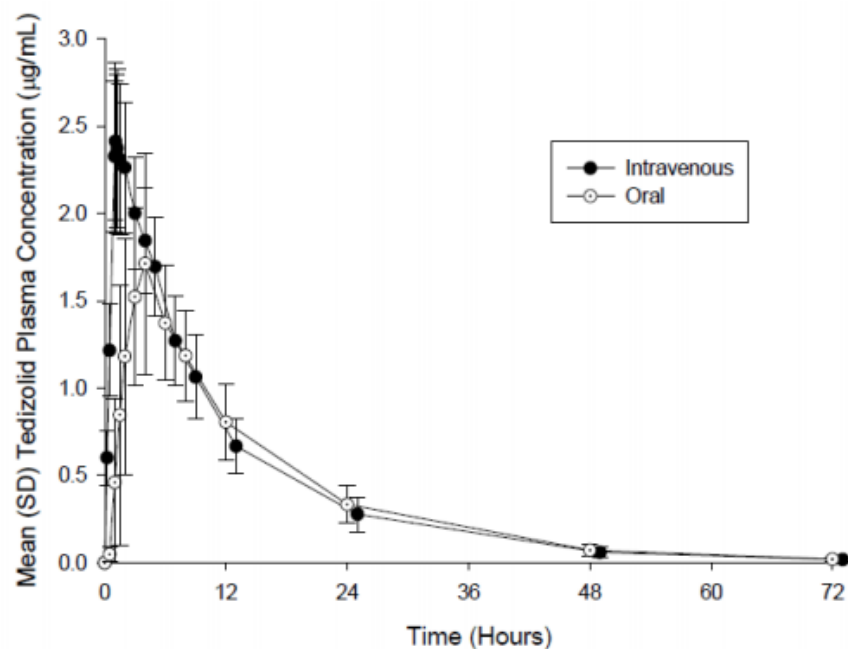
4. Breakpoints prior to harmonisation (mg/L) $S \leq R >$

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA	CLSI
General breakpoint							
	No previous breakpoints						
Species-related breakpoints							
	No previous breakpoints						
Enterobacteriaceae							
<i>Pseudomonas</i> spp.							
<i>Stenotrophomonas maltophilia</i>							
<i>Acinetobacter</i> spp.							
<i>Staphylococcus</i> spp.							S \leq 0.5, R $>$ 1
<i>Enterococcus</i> spp.							S \leq 0.5
Streptococcus groups A,B,C,G							S \leq 0.5
<i>Streptococcus pneumoniae</i>							S \leq 0.25
Viridans group streptococci							
<i>Haemophilus influenzae</i>							
<i>Moraxella catarrhalis</i>							
<i>Neisseria gonorrhoeae</i>							
<i>Neisseria meningitidis</i>							
Anaerobes, Gram-positive							
<i>Clostridium difficile</i>							
Anaerobes, Gram-negative							
<i>Helicobacter pylori</i>							
<i>Listeria monocytogenes</i>							
<i>Pasteurella multocida</i>							
<i>Campylobacter</i> spp.							
<i>Corynebacterium</i> spp.							
<i>Aerococcus</i> spp.							
<i>Kingella kingae</i>							

5. Pharmacokinetics				
Dosage (mg)	Single-dose 200mg Oral Mean (%CV or range)	Multiple-dose 200mg Oral Mean (%CV or range)	Single-dose 200mg IV Mean (%CV or range)	Multiple-dose 200mg IV Mean (%CV or range)
C _{max} (mg/L)	2.0 (35)	2.2 (27)	2.3 (26)	3.0 (23)
C _{min} (mg/L)				
T _{max} (h)	2.5 (1.0 - 8.0)	3.5 (1.0 - 6.0)	1.1 (0.9 - 1.5)	1.2 (0.9 - 1.5)
Total body clearance (L/h)	6.9 (25)	8.4 (25)	6.4 (19)	5.9 (24)
T _{1/2} (h)	12	12	12	12
AUC _{0-24h} (mg.h/L)		25.6 (33)		29.2 (21)
AUC ₀ (mg.h/L)	23.8 (29)		26.6 (20)	
AUC _∞ (mg.h/L)				
Fraction unbound (%)	10 - 30	10 - 30	10 - 30	10 - 30
Volume of distribution (L/kg)	0.14 – 0.18	--		
Comments	<ol style="list-style-type: none"> Parameters reflect the pharmacokinetic profile of tedizolid since negligible systemic exposure of tedizolid phosphate following oral or intravenous administration. Absolute oral bioavailability is approximately 91% and no dosage adjustment is recommended between intravenous and oral administration. Elimination half-life of approximately 12 hours. Following single oral administration of ¹⁴C-labeled tedizolid phosphate under fasted conditions, the majority of eliminations occurs via the liver, with 82% of the radioactive dose recovered in feces and 18% in urine (as non-circulating and microbiologically <u>inactive</u> sulfate conjugate.) 			
References	<ol style="list-style-type: none"> Sivextro (tedizolid phosphate) [Package insert], Whitehouse Station, NJ, Merck & Co., Inc., Revised July 2015 			

Tedizolid phosphate is rapidly converted by phosphatases to the microbiologically active tedizolid. The absolute bioavailability of tedizolid following oral administration of tedizolid phosphate is high (>80%); thus, the same therapeutic dosage can be used by either oral or IV delivery. Pharmacokinetic studies (PK) of tedizolid showed steady-state concentrations are achieved within 3 days with modest drug accumulation (~30%). Repeated daily oral administration of 200, 300 and 400 mg tedizolid phosphate resulted in dose proportional increases in plasma tedizolid C_{max} and AUC values. The oral clearance (CL/F) and apparent volume of distribution values for tedizolid after tedizolid phosphate administration were independent of dose and duration of exposure. Single-dose tedizolid PK appeared to predict exposure at steady state. Less than 1% of the tedizolid phosphate dose was excreted in urine as either tedizolid phosphate or active tedizolid. Figure 1 shows the tedizolid PK values following administration of tedizolid phosphate using oral and IV routes of administration. The tedizolid half-life of elimination is ~12 hours for IV or oral administration.

Figure 1 Mean Tedizolid Plasma Concentrations Following Single Oral and IV Administration of 200 mg Tedizolid Phosphate (Study TR701-107)



6. Pharmacodynamics

	Murine Pneumonia Model ¹	Murine Thigh Infection Model ²	
	<i>S. aureus</i> (MSSA; MRSA)	<i>S. aureus</i> (MSSA / MRSA): 24-h of therapy	<i>S. aureus</i> (MSSA / MRSA): 48-h of therapy
<i>f</i> AUC/MIC for bacteriostasis	20.0 ± 12.9	49.1 / 47.1	46.0 / 51.8
<i>f</i> AUC/MIC for 1-log reduction	34.6 ± 24.8	87.1 / 75.5	60.7 / 68.2
<i>f</i> AUC/MIC for 2-log reduction			92.6 / 136.7
Clinical Data			
Comments	<ul style="list-style-type: none"> • Tedizolid MIC values for <i>Staphylococcus aureus</i> ranged from 0.06 to 0.5 mg/L in the animal study¹⁻⁴ • Both animal and human data supports AUC/MIC as predictive parameter of efficacy¹⁻⁶ • In the mouse thigh infection model of <i>S. aureus</i>, anti-staphylococcal killing activity was impacted by the presence of granulocytes. In the granulocytopenic mice (neutrophil count <100 cells/mL), bacterial stasis was achieved at a human-equivalent dose of approximately 2000 mg/day; whereas, in non-neutropenic animals, stasis was achieved at a human-equivalent dose of approximately 100 mg/day.³ 		
References	<p>Acute bacterial skin and skin structure infections (ABSSSI) – Phase II and III data^{5,6}</p> <ul style="list-style-type: none"> • Assessment of PK/PD relationship to clinical outcomes • For patients with ABSSSI, target attainment simulations for 200 mg tedizolid once-daily indicated a 98.3% probability of attaining the target measure of <i>f</i>AUC/MIC = 3 against <i>S. aureus</i> strains with MIC values ≤ 0.5 mg/L.^{5,6} • The safety and efficacy of tedizolid for the treatment of neutropenic patients (neutrophil count <1000 cells/mm³) have not been evaluated.⁷ 		

7. Monte Carlo simulations and PK-PD breakpoints

Tedizolid exposure response and target attainment derived from a tedizolid population pharmacokinetic model using pooled data from seven densely and sparsely sampled phase I, II, and III clinical trials evaluating oral and intravenous tedizolid.

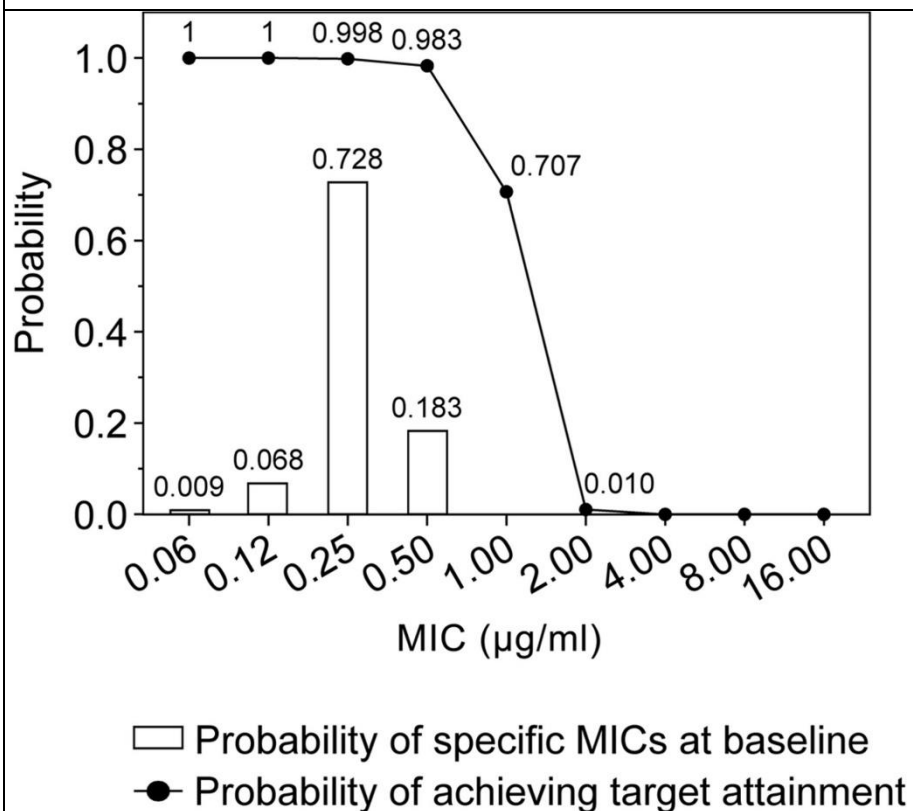


Figure 1. Probability of pharmacokinetic-pharmacodynamic target attainment for tedizolid administered at the 200-mg dose against *Staphylococcus aureus* at the $fAUC_{0-24}/MIC$ target ratio of 3 and the probabilities of the occurrence of specific MICs among the virtual patients simulated in this target attainment.

Flanagan S, Passarell J, Lu Q, Fiedler-Kelly J, Ludwig E, Prokocimer P. Tedizolid population pharmacokinetics, exposure response, and target attainment. *Antimicrob Agents Chemother* 2014; 58: 6462-6470.

8. Clinical data

Acute bacterial skin and skin structure infections (ABSSSI)

A Phase III, randomized, double-blind, noninferiority clinical trial (ESTABLISH-1) conducted from 2010 through 2011 evaluated the efficacy and safety of oral tedizolid for the treatment of ABSSSI compared to oral linezolid therapy. Patients were treated with 200 mg of tedizolid once daily for 6 days or 600 mg of linezolid twice daily for 10 days. Patients with ABSSSI included those with cellulitis/erysipelas (41%), major cutaneous abscesses (30%), and wound infections (29%). The primary endpoint was early clinical response defined as no increase from baseline lesion area at 48-72 hours after the first dose and oral temperature of $\leq 37.6^{\circ}\text{C}$, confirmed by a second temperature measurement within 24 hours in the intent-to-treat (ITT) patient population. The early clinical treatment response rates were 79.5% for the tedizolid treated patients (n = 332) and 79.4% for linezolid treated patients (n = 335), meeting the pre-specified non-inferiority margin. Similar response rates were observed for tedizolid (78.0%) and linezolid (76.1%) treated patients in a sensitivity analysis of early clinical response, defined as at least a 20% decrease from baseline lesion area at 48-72 hours after the first dose in the ITT population. Investigator-assessed clinical response rates at 7-14 days after the end of therapy were similar for tedizolid and linezolid treated patients in the ITT population (85.5% versus 86.0%) and clinical evaluable (CE) population (94.6% versus 95.4%).

Prokocimer P, De Anda C, Fang E, Mehra P, Das A.. J. Am. Med. Assoc. 2013; 309: 559-569

Acute bacterial skin and skin structure infections (ABSSSI)

A Phase III, randomized, double-blind, noninferiority clinical trial (ESTABLISH-2) conducted from 2011 through 2012 evaluated the efficacy and safety of intravenous tedizolid for the treatment of ABSSSI compared to intravenous linezolid therapy, with optional oral step-down therapy for both antibiotics. Patients were treated with 200 mg of tedizolid once daily for 6 days or 600 mg of linezolid twice daily for 10 days. Patients with ABSSSI included those with cellulitis/erysipelas (50%), major cutaneous abscesses (20%), and wound infections (30%). The primary endpoint was early clinical response defined as at least a 20% decrease from baseline lesion area at 48-72 hours after the first dose in the ITT population. The early clinical treatment response rates were 85.2% for the tedizolid treated patients (n = 332) and 82.6% for linezolid treated patients (n = 334), meeting the pre-specified non-inferiority margin. Similar response rates were observed for tedizolid (86.1%) and linezolid (84.1%) treated patients in a sensitivity analysis of early clinical response, defined as no increase from baseline lesion area at 48-72 hours after the first dose and oral temperature of $\leq 37.6^{\circ}\text{C}$, confirmed by a second temperature measurement within 24 hours in the intent-to-treat (ITT) patient population. Investigator-assessed clinical response rates at 7-14 days after the end of therapy were similar for tedizolid and linezolid treated patients in the ITT population (88.0% versus 87.7%) and clinical evaluable (CE) population (92.4% versus 96.1%).

Moran GJ, Fang E, Corey GR, Das A, De Anda C, Prokocimer P. Lancet Infect. Dis. 2014; 14: 696-705

Using pooled analysis from both phase III ABSSSI trials, the early clinical response rates by baseline pathogen for the two primary endpoints included 79.4% and 80.9% for methicillin-resistant *Staphylococcus aureus* (n = 141), 87.2% and 88.3% for methicillin-susceptible *Staphylococcus aureus* (n = 188), 81.8% and 75.8% for *Streptococcus pyogenes* (n = 33), 73.3% and 73.3% for *Streptococcus anginosus* Group (n = 30), 66.7% and 66.7% for *Streptococcus agalactiae* (n = 9), and 70.0% and 60.0% for *Enterococcus faecalis* (n=10). Clinical response rates by baseline pathogen at the post-therapy evaluation included 83.7% for methicillin-resistant *Staphylococcus aureus* (n = 141), 92.0% for methicillin-susceptible *Staphylococcus aureus* (n = 188), 90.9% for *Streptococcus pyogenes* (n = 33), 70.0% for *Streptococcus anginosus* group (n = 30), 88.9% for *Streptococcus agalactiae* (n = 9), and 70.0% for *Enterococcus faecalis* (n=10).

Abbreviations: PTE=post therapy evaluation; MIC=minimum inhibitory concentration; MRSA=methicillin-resistant *S. aureus*; MSSA=methicillin-susceptible *S. aureus*

^an, number of favorable microbiologic outcomes in the specific category; N1, number of pathogens in the specific category; Percentages are calculated as 100 x (n/N1)

^b *Streptococcus anginosus* gr.=*Streptococcus anginosus*, *Streptococcus constellatus*, and *Streptococcus intermedius*

9. Clinical breakpoints

PK-PD breakpoints	<p>PK-PD breakpoints have been determined using PK-PD data and are independent of MIC distributions of specific species. They are for use only as a guide for organisms that do not have specific breakpoints. PK-PD breakpoints have been termed “non-species-related breakpoints” but this has led to confusion and it has become clear that PK-PD breakpoints for some agents may differ for different organisms.</p> <p>For tedizolid there is insufficient evidence to set PK-PD breakpoints</p>
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	Organism group	MIC breakpoints (mg/L)		Notes
		S ≤	R >	
Species-related breakpoints	Enterobacteriaceae	-	-	1. These organisms were considered poor targets for therapy or inappropriate targets for the specified infections and for that reason did not receive breakpoints.
	<i>Pseudomonas</i> spp.	-	-	See note 1.
	<i>Stenotrophomonas maltophilia</i>	-	-	See note 1.
	<i>Acinetobacter</i> spp.	-	-	See note 1.
	<i>Staphylococcus</i> spp.	0.5	0.5	2. Isolates susceptible to linezolid can be reported susceptible to tedizolid.
	<i>Enterococcus</i> spp.	IE	IE	3. There was insufficient evidence to set breakpoints.
	Streptococcus groups A,B,C,G	0.5	0.5	See notes 2, 4. Non-susceptible isolates are rare or not yet reported. The identification and antimicrobial susceptibility test result on any such isolate must be confirmed and the isolate sent to a reference laboratory.
	<i>Streptococcus pneumoniae</i>	IE	IE	See note 3.
	Viridans group streptococci (<i>S. anginosus</i> group)	0.25	0.25	
	<i>Haemophilus influenzae</i>	-	-	See note 1.
	<i>Moraxella catarrhalis</i>	-	-	See note 1.
	<i>Neisseria gonorrhoeae</i>	-	-	See note 1.
	<i>Neisseria meningitidis</i>	-	-	See note 1.
	Anaerobes, Gram-positive	-	-	See note 1.
	<i>Clostridium difficile</i>	-	-	See note 1.
	Anaerobes, Gram-negative	-	-	See note 1.
	<i>Helicobacter pylori</i>	-	-	See note 1.
<i>Listeria monocytogenes</i>	-	-	See note 1.	
<i>Pasteurella multocida</i>	-	-	See note 1.	

	<i>Campylobacter</i> spp.	-	-	See note 1.
	<i>Corynebacterium</i> spp.	-	-	See note 1.
	<i>Aerococcus</i> spp.	-	-	See note 1.
	<i>Kingella kingae</i>	-	-	See note 1.
Clinical qualifications	Breakpoints apply only to the treatment of acute bacterial skin and skin structure infections (ABSSSI in adults.			
Dosage	Breakpoints apply to oral or iv dosage regimen of tedizolid 200 mg once-daily for 6 days.			
Additional comment	<p>For <i>Staphylococcus</i> spp. and streptococcus groups A,B,C,G , isolates susceptible to linezolid by disk diffusion can be reported susceptible to tedizolid. For isolates resistant to linezolid, perform an MIC test.</p> <p>For Viridans group streptococci an MIC method should be used for susceptibility testing.</p>			

10. Exceptions noted for individual national committees

None.