

# Relative Potency of TR-700, the Active Moiety of Prodrug TR-701 against Selected Bacterial Pathogens and Provisional Disk Test Criteria

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## Abstract

**Background:** TR-701, a promising new oxazolidinone, is a prodrug under development by Trius Therapeutics; the active moiety is TR-700.  
**Methods:** The in vitro activity of TR-700 was compared to that of linezolid (Lnz), cefotaxime (Ctx) and levofloxacin (Levo) against 900 bacterial pathogens representing 3 genera. CLSI broth microdilution and disk diffusion methodologies were used. Tentative microbiological MIC breakpoints are proposed. A 20 µg TR-700 disk was used to propose tentative disk diffusion breakpoints. **Results:** MIC<sub>90s</sub> (µg/ml) and disk diffusion breakpoints for 5 groups of microorganisms were:

Table 1. MIC<sub>90s</sub> and Proposed Breakpoints

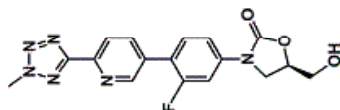
Species	MIC <sub>90</sub> µg/ml				TR-700 Proposed Breakpoints	
	TR-700	Lnz	Ctx	Levo	MIC (µg/ml) S, I, R	Disk (mm) S, I, R
Enterococci (n=203)	0.5	2	>64	>16	≤2, -, -	≥15, -, -
Staphylococci (n=336)	0.5	2	>64	>16	≤2, 4, ≥8	≥18, 15-17, ≤14
Streptococci (n=361)	0.25	16	1	1	≤2, -, -	≥15, -, -

**Conclusions:** TR-700 was very active against the majority of the strains tested. TR-700 tended to be 4- to 64-fold more active than Lnz, 4- to 256-fold more active than Ctx, and 4- to >64-fold more active than Levo against all species tested. Tentative disk diffusion breakpoints are proposed for the 20 µg TR-700 disk. Provisional interpretive criteria must await pharmacokinetic and clinical information.

## Introduction

- TR-700 (Figure 1) is a new oxazolidinone antimicrobial currently under clinical development.
- A representative sample of 900 recent clinical isolates and selected stock cultures were tested.
- Broth microdilution tests compared TR-700 to Lnz, Ctx and Levo.
- MICs were determined along with disk diffusion zone diameters in order to propose tentative disk diffusion breakpoints.

Figure 1. Structure of TR-700, the active moiety of TR-701.



## Materials & Methods

•Broth microdilution and disk diffusion tests were performed according to the latest CLSI documents M7-A7<sup>1</sup>, 2006 and M2-A9<sup>2</sup>, 2006.

•Recent clinical isolates were selected to represent selected species. For the less common species, stock cultures were utilized.

•MIC trays were produced at CMI using cation adjusted Mueller-Hinton broth (CAMHB, DIFCO lot #7306781). The medium was supplemented with lysed horse blood (Hemostat lot #H05287) for testing the streptococci.

•Disk diffusion plates were purchased from commercial suppliers.

•TR-700 and Lnz zone diameters were read using transmitted light as recommended by the CLSI. Zone diameters for all other genera were read using reflected light as specified by the CLSI.

•TR-700 (Lot #DP-70-1465/wt) was obtained from Trius Therapeutics, Inc.

•Lnz (lot#1000891018) was obtained from Pfizer, Inc.

•Ctx (lot #036K1623) and Levo (lot#1333515) were purchased from Sigma.

•Quality Control was performed on each day of testing.

•All microorganisms were tested by disk diffusion method using commercial disks and a 20 µg TR-700 disk prepared by CMI

## Results

•The antimicrobial activity of TR-700 against all isolates is summarized in Tables 1 & 2.

•TR-700 was very active against the majority of the strains of methicillin-susceptible and methicillin-resistant staphylococci, α- and β-hemolytic streptococci.

•The TR-700 MIC<sub>90s</sub> for each of these groups was ≤1 µg/ml.

•TR-700 was 4- fold more active than linezolid against the staphylococci and enterococci.

•When compared to Ctx and Levo, TR-700 was 8- to >128-fold more active against all of the groups tested.

Table 2. MIC<sub>50s</sub> & MIC<sub>90s</sub>

Species	N	Drug	MIC <sub>50</sub>	MIC <sub>90</sub>
All <i>Staphylococcus</i> spp. Combined	338	TR-700	0.25	0.5
		Cefotaxime	4	>64
		Levofloxacin	0.5	>16
		Linezolid	2	2
All <i>S. aureus</i> Combined	234	TR-700	0.5	0.5
		Cefotaxime	8	>64
		Levofloxacin	4	>16
		Linezolid	2	2
<i>S. aureus</i> methicillin-susceptible	105	TR-700	0.25	0.5
		Cefotaxime	2	2
		Levofloxacin	0.25	4
		Linezolid	2	2
<i>S. aureus</i> methicillin-resistant	129	TR-700	0.5	1
		Cefotaxime	16	>64
		Levofloxacin	8	>16
		Linezolid	2	4
<i>S. aureus</i> linezolid-resistant	13	TR-700	4	8
		Cefotaxime	>64	>64
		Levofloxacin	>16	>16
		Linezolid	>8	>8
<i>S. aureus</i> vancomycin-non-susceptible	32	TR-700	0.25	1
		Cefotaxime	>64	>64
		Levofloxacin	16	>16
		Linezolid	2	4
All Coagulase-Negative Staphylococci Combined*	104	TR-700	0.25	0.5
		Cefotaxime	2	>64
		Levofloxacin	0.5	>16
		Linezolid	1	2
All Methicillin-Resistant Coagulase-Negative Staphylococci Combined	58	TR-700	0.25	0.5
		Cefotaxime	8	>64
		Levofloxacin	8	>16
		Linezolid	1	4
All Methicillin-Susceptible Coagulase-Negative Staphylococci Combined	46	TR-700	0.25	0.5
		Cefotaxime	0.5	2
		Levofloxacin	0.25	0.5
		Linezolid	1	2
All Enterococci Combined	203	TR-700	0.5	0.5
		Cefotaxime	>64	>64
		Levofloxacin	>16	>16
		Linezolid	2	2
<i>E. faecalis</i> vancomycin-resistant	45	TR-700	0.5	0.5
		Cefotaxime	>64	>64
		Levofloxacin	>16	>16
		Linezolid	2	2
<i>E. faecalis</i> vancomycin-susceptible	54	TR-700	0.5	0.5
		Cefotaxime	>64	>64
		Levofloxacin	1	>16
		Linezolid	2	2
<i>E. faecium</i> vancomycin-resistant	52	TR-700	0.5	0.5
		Cefotaxime	>64	>64
		Levofloxacin	>16	>16
		Linezolid	2	4
<i>E. faecium</i> vancomycin-susceptible	52	TR-700	0.5	0.5
		Cefotaxime	>64	>64
		Levofloxacin	4	>16
		Linezolid	2	2
All Streptococcal spp. Combined	361	TR-700	0.25	0.25
		Cefotaxime	0.03	1
		Levofloxacin	1	1
		Linezolid	1	2
All <i>Streptococcus pneumoniae</i> Strains Combined	133	TR-700	0.25	0.25
		Cefotaxime	0.12	2
		Levofloxacin	1	1
		Linezolid	1	2
<i>S. pneumoniae</i> penicillin-susceptible	53	TR-700	0.25	0.25
		Cefotaxime	0.015	0.03
		Levofloxacin	1	1
		Linezolid	1	2
<i>S. pneumoniae</i> penicillin-intermediate	26	TR-700	0.25	0.5
		Cefotaxime	0.12	0.5
		Levofloxacin	1	1
		Linezolid	1	2
<i>S. pneumoniae</i> penicillin-resistant	54	TR-700	0.25	0.25
		Cefotaxime	1	8
		Levofloxacin	1	1
		Linezolid	1	2
All β-hemolytic Streptococcal Strains Combined (101 <i>S. agalactiae</i> , 101 <i>S. pyogenes</i> )	202	TR-700	0.25	0.25
		Cefotaxime	0.03	0.06
		Levofloxacin	0.5	1
		Linezolid	1	2
<i>S. viridans</i> group	30	TR-700	0.25	0.25
		Cefotaxime	0.12	0.5
		Levofloxacin	1	2
		Linezolid	2	2

\*54 *S. epidermidis*, 14 *S. haemolyticus*, 10 *S. hominis*, 7 *S. lugdunensis*, 13 *S. saprophyticus*, 6 CNS-Nos

## Figures 2-4

Figure 2. TR-700 MIC vs. TR-700 20 µg Disk 24 hr (Transmitted Light)

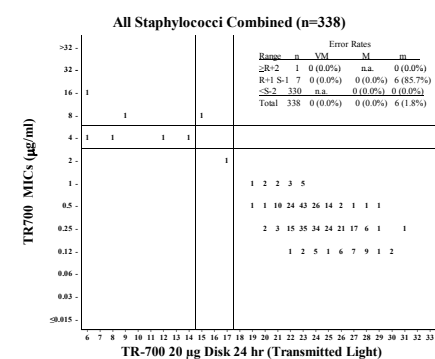


Figure 3. TR-700 MIC vs. TR-700 20 µg Disk 16-18 hr (Reflected Light)

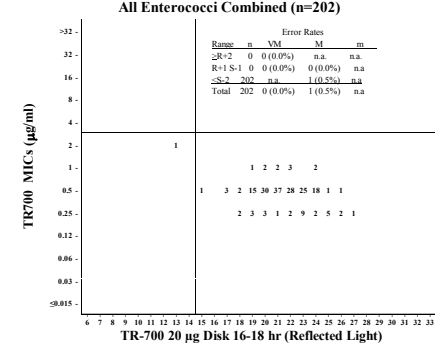
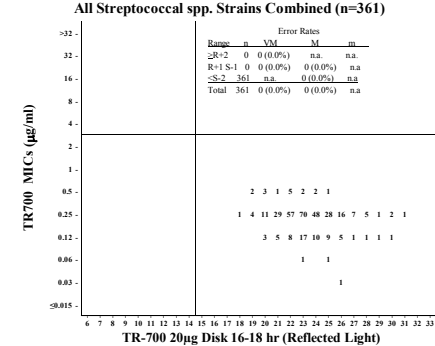


Figure 4. TR-700 MIC vs. TR-700 20µg Disk 16-18 hr (Reflected Light)



## Results (continued)

•Scattergrams showing the distribution of MICs plotted against the corresponding zone diameters can be found in Figures 2-4.

•Based upon “presumptive” MIC breakpoints, disk diffusion breakpoints are proposed for each of the groups tested using the 20 µg disk

•All of the quality control values observed for the comparator drugs were within the ranges established by the CLSI.

## Conclusions

•TR-700 was very active against the majority of the strains of methicillin-susceptible and methicillin-resistant staphylococci and streptococci.

•TR-700 was 4-fold more active than linezolid against the staphylococci and enterococci.

•TR-700 was 8- to >128-fold more active against all of the groups when compared to cefotaxime and levofloxacin

•Tentative MIC and disk diffusion breakpoints are presented in Table 3.

Table 3. Tentative “Microbiological” MIC and Disk Diffusion Breakpoints

Species	MIC Breakpoints (µg/ml) (S, I, R)	Disk Diffusion Breakpoints using a 20 µg Disk (S, I, R)
Enterococci	≤2 for S with no I or R categories	≥15 mm for S with no I or R categories
Staphylococci	≤2, 4, ≥8	≥18, 15-17, ≤14 mm
Streptococci including <i>S. pneumoniae</i> , β-streptococci and α-streptococci	≤2 for S with no I or R categories	≥15 mm for S with no I or R categories

## References

1. Clinical and Laboratory Standards Institute. *Methods for dilution antimicrobial susceptibility tests for Bacteria that Grow Aerobically; Approved Standard-7th Edition*. CLSI Document M7-A7. 2006.
2. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard—9th Edition*. CLSI Document M2-A9. 2006.

## Acknowledgement

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