

Doripenem: Rationale for EUCAST Clinical Breakpoints

Current version	2.0	January 2024
Previous versions	1.0	June 2009

Introduction

Doripenem is a carbapenem, available only for parenteral use.

Doripenem is relevant for therapy of nosocomial pneumonia, including ventilator-associated pneumonia, complicated intra-abdominal infections, and complicated urinary tract infections, including complicated and uncomplicated pyelonephritis, tissue infections caused by *Staphylococcus* spp., *Streptococcus* spp. (including *Streptococcus pneumoniae*), *Haemophilus influenzae*, *Enterobacterales* and *Pseudomonas* spp. Doripenem can be used in the treatment of both Gram-positive and Gram-negative infections.

Doripenem is not considered active against *Stenotrophomonas maltophilia* and *Enterococcus* spp.

Resistance to doripenem is conferred by PBP changes also mediating high-level penicillin resistance in *S. pneumoniae*, by PBP changes mediating β -lactam resistance in *H. influenzae*, and by production of carbapenemases in *Pseudomonas* spp. and *Enterobacterales*. Doripenem is not affected by classical ESBL and AmpC beta-lactamases in *Enterobacterales*. In *Enterobacterales*, combinations of an ESBL or AmpC enzyme and impermeability confer reduced susceptibility to doripenem, often without causing clinical resistance. In *P. aeruginosa* porin loss and alteration in efflux pumps may also reduce doripenem susceptibility.

This version is extracted and updated from version 1.0, and will be the format for future updates. Previous versions are available on request.

Dosages related to clinical breakpoints

Standard dosage: 0.5 g x 3 iv over 1 hour

High dosage: 1 g x 3 iv over 1 hour

Healthcare- and ventilator-associated pneumonia due to non-fermenting gram-negative pathogens (such as *Pseudomonas* spp. and *Acinetobacter* spp.):

1 g x 3 iv over 4 hours

MIC distributions and epidemiological cut-off (ECOFF) values

MIC distributions and ECOFFs can be found at <https://mic.eucast.org/Eucast2/SearchController/search.jsp?action=init>

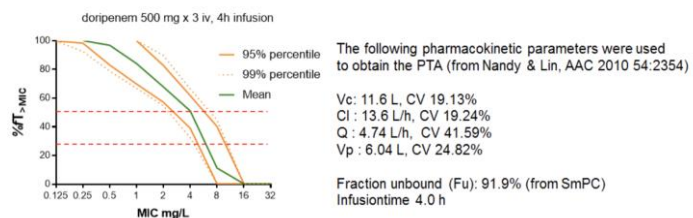
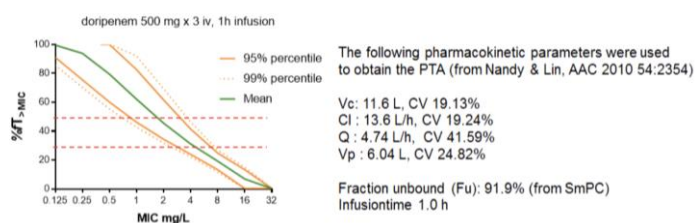
Pharmacokinetics

PK parameter	Pharmacological studies		Efficacy studies	
Dosage	0.5 g x 3 iv 1h infusion	0.5 g x 3 iv 4h infusion		
C _{max} (mg/L)	20-25	8-10		
C _{min} (mg/L)	<0.1	<0.1		
Total body clearance (L/h)	15	14.5		
T _{1/2} (h), mean (range)	(0.95 - 1.15)	(0.95 - 1.23)		
AUC ₀₋₁₂ (mg.h/L)				
AUC ₀₋₂₄ (mg.h/L)	100	100		
AUC _{0-∞} (mg.h/L)				
Fraction unbound (%)	92	92		
Volume of distribution _{ss} (L)	17-20	18 - 20		

Pharmacodynamics

Index	Neutropenic mouse thigh				
	Enterobacterales, <i>P. aeruginosa</i>	<i>S. pneumoniae</i>	<i>S. aureus</i>		
	Range	Range	Range		
f%T>MIC for bacteriostasis	20-45	15-20	10-30		
f%T>MIC for 1-log ₁₀ kill	35-55	25-40	15-40		

Monte Carlo simulations



Commented [AM1]: Here is an example of where Q etc is. PK people will understand. But therefore I wondered who needs to understand. I am fine with leaving it without explanation.

Clinical studies

Doripenem registration studies have shown clinical and microbiological non-inferiority in treatment of nosocomial pneumonia, including ventilator-associated pneumonia (comparators piperacillin-tazobactam and imipenem), complicated intra-abdominal infections (comparator meropenem), and complicated urinary tract infections, including complicated and uncomplicated pyelonephritis (comparator levofloxacin).

The results of a multi-centre comparative clinical trial in nosocomial pneumonia (incl. VAP) raised concerns (Kollef et al., Crit Care 2012). There was a special text box about this trial in the EMA Summary of Product Characteristics

The FDA responded to the results of this trial by withdrawing doripenem's approval for NP/VAP (<https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-approves-label-changes-antibacterial-doribax-doripenem-describing>).

Of note, this trial used doripenem at a dose of 1 g every 8 hours with a 4-hour infusion time, the regimen giving the highest exposure, compared to imipenem-cilastatin (1 g x 3, 1-h infusion).

Clinical breakpoints

The clinical breakpoints for doripenem can be found in the most recent version of the Breakpoint tables: https://www.eucast.org/clinical_breakpoints

References

- Bhavnani SM, Hammel JP, Cirincione BB, Wikler MA, Ambrose PG. Use of pharmacokinetic-pharmacodynamic target attainment analyses to support phase 2 and 3 dosing strategies for doripenem., *Antimicrob Agents Chemother* 2005; 49:3944
- EMA: Doribax-EPAR-product -information. https://www.ema.europa.eu/en/documents/product-information/doribax-epar-product-information_en.pdf
- Mazzei T. The pharmacokinetics and pharmacodynamics of the carbapenemes: focus on doripenem. *J Chemother.* 2010 Aug;22(4):219-25.
- Paterson DL, Depestele DD. Doripenem. *Clin Infect Dis.* 2009 Jul 15;49(2):291-8.