

Doripenem	Rationale for the EUCAST clinical breakpoints, version 1.0	1 st June 2009
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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*, Enterobacteriaceae 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 Enterobacteriaceae. Doripenem is not affected by classical ESBL and AmpC β -lactamases in Enterobacteriaceae. In Enterobacteriaceae, 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.

1. Dosage

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose (mg)						
Maximum dose schedule (mg)						
Available formulations ¹	Not registered	Not registered	Not registered	Not registered	Not registered	Not registered

¹ Not registered at the time breakpoints were assessed. Clinical breakpoints were determined for parenteral use of doripenem 500 mg x 3 iv infused over one hour and four hours.

2. MIC distributions and epidemiological cut-off (ECOFF) values

	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>Acinetobacter baumannii</i>	0	0	0	0	2	21	104	249	219	301	275	175	234	351	1	0	0	0	0	1
<i>Acinetobacter calcoaceticus</i>	0	0	0	0	0	4	3	4	4	3	2	2	5	6	0	0	0	0	0	1
<i>Acinetobacter lwoffii</i>	0	0	0	0	0	37	38	35	26	4	4	0	6	3	0	0	0	0	0	1
<i>Acinetobacter</i> spp.	0	0	0	6	25	133	317	491	434	428	382	243	321	478	38	44	0	0	0	1
<i>Aeromonas hydrophila</i>	0	0	0	0	0	32	5	3	25	16	6	3	1	1	0	0	0	0	0	IE
<i>Aeromonas</i> spp.	0	0	0	0	0	54	12	10	36	28	14	9	1	1	0	0	0	0	0	IE
<i>Alcaligenes xylosoxidans</i>	0	0	0	0	0	0	3	4	20	6	7	9	2	6	0	0	0	0	0	IE
<i>Bacteroides fragilis</i>	0	0	0	0	0	3	30	95	7	3	0	4	3	3	0	0	0	0	0	1
<i>Bacteroides fragilis</i> group	0	0	0	0	0	5	52	250	54	11	2	5	6	3	0	0	0	0	0	1
<i>Bacteroides thetaiotaomicron</i>	0	0	0	0	0	0	5	54	17	3	1	0	1	0	0	0	0	0	0	1
<i>Citrobacter freundii</i>	0	0	1	5	7	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0.12
<i>Citrobacter koseri</i>	0	0	2	7	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.12
<i>Citrobacter</i> spp.	0	0	75	445	316	44	13	2	1	0	0	0	0	0	0	0	0	0	0	0.12
<i>Corynebacterium</i> spp.	0	0	0	0	0	24	20	23	25	8	6	4	3	26	0	0	0	0	0	IE
<i>Enterobacter aerogenes</i>	0	0	0	3	7	4	1	0	0	0	0	0	0	0	0	0	0	0	0	0.12
<i>Enterobacter cloacae</i>	0	0	0	125	457	274	157	51	15	4	1	1	0	0	0	0	0	0	0	0.12
<i>Enterobacter</i> spp.	0	0	0	19	313	293	113	62	28	9	2	4	2	6	0	0	0	0	0	0.12
<i>Enterococcus avium</i>	0	0	0	0	0	2	0	0	1	7	16	20	8	14	0	0	0	0	0	ND
<i>Enterococcus faecalis</i>	0	0	0	0	1	12	1	13	69	181	1526	4140	1313	338	2	0	0	0	0	16
<i>Enterococcus faecium</i>	0	0	0	1	0	1	0	2	0	8	14	27	101	2461	326	43	17	21	0	64
<i>Enterococcus gallinarum</i>	0	0	0	0	0	0	2	0	1	7	17	24	13	33	0	0	0	0	0	IE
<i>Enterococcus</i> spp.	0	0	0	2	1	26	4	19	70	147	1545	3910	1366	2894	6	170	0	0	0	--
<i>Escherichia coli</i>	0	0	6	1775	3087	203	23	11	3	3	0	1	0	0	0	0	0	0	0	0.12
<i>Haemophilus influenzae</i>	0	0	14	21	100	426	366	139	104	32	12	4	0	0	0	0	0	0	0	0.5
<i>Klebsiella oxytoca</i>	0	0	0	7	45	8	0	1	0	0	0	0	0	0	0	0	0	0	0	0.12
<i>Klebsiella pneumoniae</i>	0	0	1	167	1256	683	119	13	3	0	3	4	4	0	1	0	0	0	0	0.12
<i>Klebsiella</i> spp.	0	0	0	4	470	286	32	9	3	1	3	4	0	1	3	0	0	0	0	0.12
<i>Moraxella catarrhalis</i>	0	0	7	15	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	IE
<i>Morganella morganii</i>	0	0	0	0	1	45	161	227	88	9	0	0	0	0	0	0	0	0	0	1
<i>Proteus mirabilis</i>	0	0	0	2	75	1157	2099	1365	206	26	10	0	0	4	0	0	0	0	0	0.5
<i>Proteus vulgaris</i>	0	0	0	0	0	45	119	58	5	0	0	0	0	0	0	0	0	0	0	0.5
<i>Providencia stuartii</i>	0	0	0	0	0	19	16	14	1	2	0	0	0	0	0	0	0	0	0	0.5
<i>Pseudomonas aeruginosa</i>	0	0	0	5	45	489	1531	2089	2148	1407	779	866	651	576	45	7	0	0	0	1

	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>Serratia liquefaciens</i>	0	0	0	0	0	2	14	6	3	0	0	0	0	0	0	0	0	0	0	0.5
<i>Serratia marcescens</i>	0	0	0	3	15	518	1221	362	40	4	0	1	2	7	0	3	0	0	0	0.5
<i>Serratia</i> spp.	0	0	0	0	0	391	948	270	35	3	0	1	1	7	0	0	0	0	0	0.5
<i>Staphylococcus aureus</i>	0	0	0	35	1159	1260	61	7	3	1	1	0	0	0	0	0	0	0	0	0.12
<i>Staphylococcus aureus</i> MRSA	0	0	0	4	31	230	772	1432	1936	1651	1121	1147	1278	3094	501	73	0	0	0	--
<i>Staphylococcus aureus</i> MSSA	0	0	0	137	635	91	15	11	8	4	2	0	0	0	0	0	0	0	0	0.12
<i>Staphylococcus coagulase</i> -ve	0	0	0	11	17	12	11	6	14	18	10	8	10	6	1	0	0	0	0	0.12
<i>Staphylococcus epidermidis</i>	0	0	0	12	46	9	0	1	0	0	1	0	0	0	0	0	0	0	0	0.12
<i>Staphylococcus lugdunensis</i>	0	0	0	0	0	18	25	19	0	0	3	1	1	1	0	0	0	0	0	0.25
<i>Staphylococcus saprophyticus</i>	0	0	0	0	0	21	20	1	2	2	1	3	3	7	0	0	0	0	0	0.25
<i>Stenotrophomonas maltophilia</i>	0	0	0	0	0	0	0	0	3	3	1	6	18	938	0	0	0	0	0	IE
<i>Streptococcus agalactiae</i>	0	3	15	46	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.032
<i>Streptococcus anginosus</i>	0	0	0	10	9	6	0	0	0	1	0	0	0	0	0	0	0	0	0	IE
<i>Streptococcus bovis</i>	0	1	11	8	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	IE
<i>Streptococcus</i> group G	0	54	5	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	IE
<i>Streptococcus mitis</i>	0	4	3	1	5	0	1	0	0	0	0	0	0	0	0	0	0	0	0	IE
<i>Streptococcus oralis</i>	0	7	20	17	10	3	4	0	2	0	0	0	0	0	0	0	0	0	0	IE
<i>Streptococcus pneumoniae</i>	0	186	31	2	2	0	0	8	1	0	0	0	0	0	0	0	0	0	0	0.032
<i>Streptococcus pyogenes</i>	0	78	6	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.032

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

3. Breakpoints prior to harmonisation¹ (mg/L) S_≤/R>							
	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA	CLSI
General breakpoints							
Species related breakpoints							

¹Doripenem is a new agent so no breakpoints were available prior to harmonisation.

4. Pharmacokinetics

Dosage (mg)	500 mg x 3 iv 1h infusion	500 mg 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 _½ (h), mean (range)	(0.95 - 1.15)	(0.95 -1.23)
AUC _{24h} (mg.h/L)	100	100
Fraction unbound (%)	92	92
Volume of distribution (L/kg)	17-20	18 - 20
Comments	<ul style="list-style-type: none">Two values are given where references differ. Cells are left empty when data are not readily available.	
References	<ul style="list-style-type: none">Data on File, Johnson & JohnsonBhavnani et al., Antimicrob Agents Chemother 2005; 49:3944	

5. Pharmacodynamics

	Enterobacteriaceae, <i>Pseudomonas aeruginosa</i>	<i>S. pneumoniae</i>	<i>S.aureus</i>
% fT>MIC for bacteriostasis (experimental)	20-45	15-20	10-30
% fT>MIC for 2 log reduction (experimental)	35-55	25-40	15-40
%fT>MIC from clinical data	54		
Comments	<ul style="list-style-type: none"> • Pk/Pd data for carbapenems are presented as class effects. There are no indications that the Pk/Pd properties differ between carbapenem agents. • Cells are left empty when data are not readily available. 		
References	<ul style="list-style-type: none"> • DeRyke CA, et al. Antimicrob Agents Chemother 2007; 51:1481. • Li C, et al. Antimicrob Agents Chemother 2007; 51:1725 • Maglio D, et al. Antimicrob Agents Chemother 2005; 49:276 • Xuan D, et al. Antimicrob Agents Chemother 2002; 46:2990 • Andes D, et al. ICAAC 2003 abstr. A308 • Takata T, et al., J Infect Chemother 2004; 10:76 • Sugihara K, et al. ICAAC 2008 abstr. A027 • MacGowan AP et al, Antimicrob. Agents Chemother. 2008, 52: 1401-06 		

6. Monte Carlo simulations and Pk/Pd breakpoints

Probabilities of Target Attainment (PTA) for 500 mg x 3 iv are shown in Figure 1.

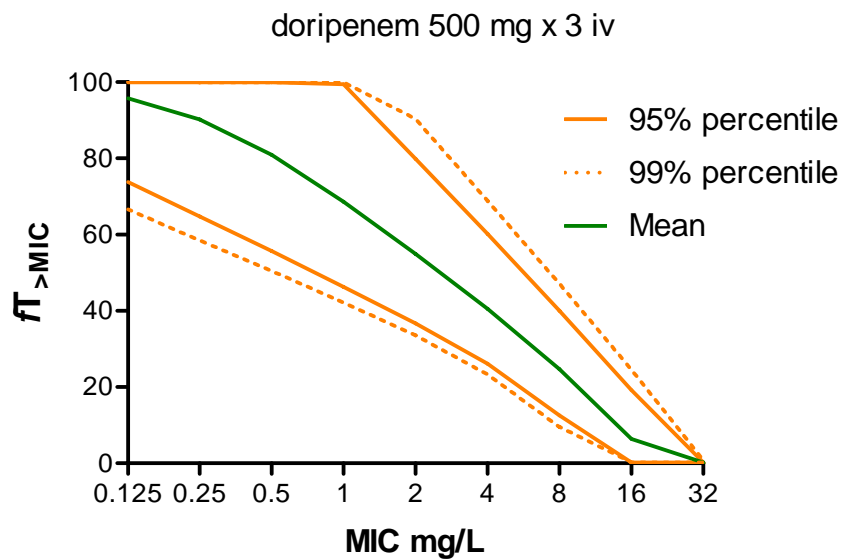


Figure 1. Probabilities of target attainment for doripenem 500 mg x 3 iv.

The following pharmacokinetic parameters were used to obtain the PTA:
Volume of distribution (Vd): 18 L, CV 20%
Elimination half-life (t): 1.05 h, CV 20%
Fraction unbound (Fu): 92 %
Infusion time: 1.0 h

7. Clinical data

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).

8. Clinical breakpoints

Non-species-related breakpoints	<p>Non-species related breakpoints have been determined using Pk/Pd data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints.</p> <p>A 2 log drop in viable Gram-negative organisms in animal model infections requires 40 - 50% $fT > MIC$. The 95% confidence interval of the 500 mg dose administered by 1h infusion results in an S/I breakpoint of 1 mg/L. The I/R breakpoint of 4 mg/L is based on the 4 h infusion time.</p> <p>These breakpoints render wild type Enterobacteriaceae, <i>Pseudomonas</i> spp. and <i>Acinetobacter</i> spp. susceptible.</p>
Species-related breakpoints	<p>For <i>Streptococcus pneumoniae</i>, streptococci groups A, B, C, G, other streptococci, <i>Haemophilus</i> spp., <i>Moraxella catarrhalis</i> and anaerobes, breakpoints were set at 1/1 mg/L as strains with MIC values above 1 mg/L are rare or not yet reported.</p> <p>Susceptibility of staphylococci is inferred from the methicillin susceptibility.</p>
Species without breakpoints	<p><i>Enterococcus</i> spp. were considered poor targets for doripenem therapy and for that reason did not receive breakpoints.</p> <p>There was considered to be insufficient evidence to set breakpoints for <i>Neisseria</i> spp.</p>
Clinical qualifications	
Dosage	<p>EUCAST breakpoints apply to doripenem 500 mg x 3 daily administered intravenously over 1 hour as the lowest dose. 500 mg x 3 daily administered over 4 hours was taken into consideration for severe infections and in setting the I/R breakpoint.</p>
Additional comment	

9. Current EUCAST breakpoints

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

10. Exceptions noted for individual national committees
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None
