

<b>Ertapenem</b>	<b>Rationale for the EUCAST clinical breakpoints, version 1.3</b>	<b>1<sup>st</sup> June 2009</b>
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## Introduction

Ertapenem is a carbapenem, available only for parenteral use.

Ertapenem is relevant for therapy of septicaemia, post-operative sepsis, nosocomial pneumonia, community acquired pneumonia, and complicated skin and soft tissue infections caused by *Staphylococcus* spp., *Streptococcus* spp. (including *Streptococcus pneumoniae*), *Haemophilus influenzae* and Enterobacteriaceae. Ertapenem can be used in the treatment of both Gram-positive and Gram-negative infections.

Ertapenem is not considered active against *Pseudomonas* spp, *Stenotrophomonas maltophilia*, *Acinetobacter* spp. and *Enterococcus* spp.

Resistance to ertapenem is conferred by PBP changes also mediating high-level penicillin resistance in *S. pneumoniae*, by PBP changes mediating  $\beta$ -lactam resistance in *H. Influenzae*, and by production of carbapenemases in *Pseudomonas* spp. and Enterobacteriaceae. Ertapenem is affected by some classical ESBL and AmpC  $\beta$ -lactamases in Enterobacteriaceae but organisms remain clinically susceptible. In Enterobacteriaceae resistance may be conferred by combinations of an ESBL or AmpC enzyme and impermeability. In *Pseudomonas aeruginosa*, porin loss and alteration in efflux pumps may also reduce ertapenem susceptibility.

## 1. Dosage

	<b>BSAC</b>	<b>CA-SFM</b>	<b>CRG</b>	<b>DIN</b>	<b>NWGA</b>	<b>SRGA</b>
Most common dose (mg)	1g x 1	1g x 1	1g x 1	1g x 1	1g x 1	1g x 1
Maximum dose schedule (mg)	1g x 1	1g x 1	1g x 1	1g x 1	1g x 1	1g x 1
Available formulations	iv	iv	iv	iv	iv	iv



	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>Providencia rettgeri</i>	0	0	2	10	3	6	9	6	3	0	0	0	1	0	0	0	0	0	0	0.064
<i>Providencia</i> spp.	0	0	14	21	29	11	10	18	4	1	1	0	0	0	0	0	0	0	0	0.064
<i>Providencia stuartii</i>	0	0	2	16	11	16	15	7	0	1	0	0	0	0	0	0	0	0	0	0.064
<i>Pseudomonas aeruginosa</i>	0	0	1	2	2	1	21	21	72	178	304	319	286	267	208	218	104	0	105	ND
<i>Salmonella</i> spp.	0	0	158	122	25	5	2	3	0	0	1	0	0	0	0	0	0	0	0	0.064
<i>Serratia marcescens</i>	0	0	4	68	43	33	16	18	8	0	1	1	0	0	0	0	0	0	0	0.064
<i>Serratia</i> spp.	0	33	33	80	142	57	41	10	5	10	3	1	0	0	0	0	0	0	0	0.064
<i>Shigella</i> spp.	0	0	129	50	7	1	3	3	3	0	0	0	0	0	0	0	0	0	0	0.064
<i>Staphylococcus aureus</i>	0	0	5	2	7	65	575	262	41	14	7	16	17	16	16	7	11	10	0	1
<i>Staphylococcus capitis</i>	0	0	0	0	0	0	0	5	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Staphylococcus coagulase -ve</i>	0	0	0	0	4	21	97	125	52	32	25	20	18	25	2	0	0	0	0	1
<i>Staphylococcus epidermidis</i>	0	0	0	0	8	12	39	29	12	27	15	25	7	1	5	2	6	15	0	1
<i>Staphylococcus haemolyticus</i>	0	0	0	0	0	0	1	1	7	0	0	3	5	0	3	2	4	6	0	ND
<i>Staphylococcus saprophyticus</i>	0	0	0	0	0	0	0	2	6	37	14	0	2	0	0	0	0	0	0	ND
<i>Stenotrophomonas maltophilia</i>	0	0	0	0	0	1	0	0	0	4	20	14	21	0	0	0	0	0	0	ND
<i>Streptococcus agalactiae</i>	0	0	31	33	220	181	37	3	1	0	0	0	2	2	0	0	0	0	0	ND
<i>Streptococcus anginosus</i>	0	0	0	0	1	0	13	5	4	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus</i> group G	0	0	0	76	19	1	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus oralis</i>	0	0	0	18	34	21	7	6	4	3	4	1	0	0	0	0	0	0	0	ND
<i>Streptococcus pneumoniae</i>	99	526	830	592	145	49	55	107	84	11	4	2	1	1	0	0	0	0	0	ND
<i>Streptococcus pyogenes</i>	0	3	204	329	65	16	7	3	1	0	0	0	0	0	0	0	0	0	0	ND

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 harmonisation (mg/L) S<sub>≤</sub>/R<sub>></sub>

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA	CLSI
<b>General breakpoints</b>							
						1/2	
<b>Species related breakpoints</b>							
<i>Staphylococcus</i> spp.							
<i>Streptococcus</i> spp.							1/-
<i>Streptococcus pneumoniae</i>	2/2					0.25/0.5	1/-
<i>Enterococcus</i> spp.	0.03/1						
Enterobacteriaceae						0.5/2	2/4
<i>Pseudomonas</i> spp.	2/2						
<i>Acinetobacter</i> spp.							
<i>Haemophilus</i> spp.	2/2						0.5/-
<i>Moraxella</i> spp.	2/2						0.5/-
<i>Neisseria meningitidis</i>							
<i>Neisseria gonorrhoeae</i>	2/2						
<i>Pasteurella multocida</i>							
Gram-negative anaerobes							
<i>Campylobacter</i> spp.							4/8

#### 4. Pharmacokinetics

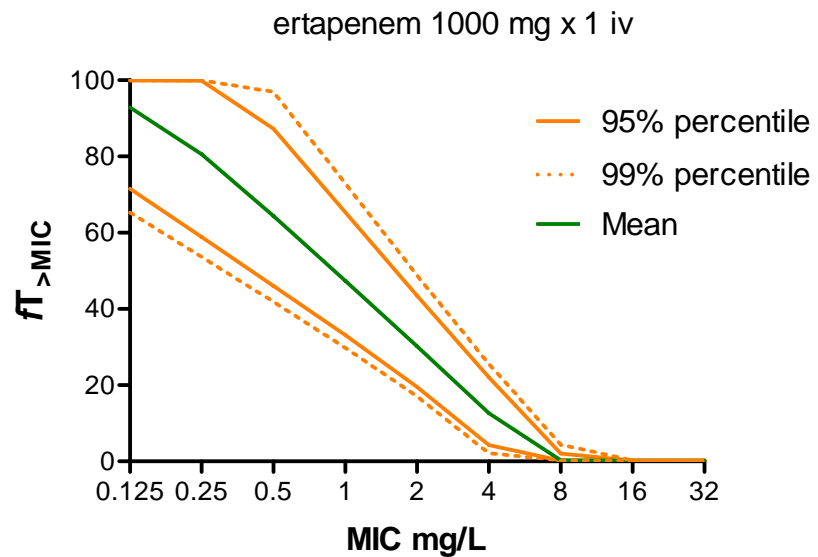
Dosage (mg)	<b>1 g x 1</b>	
C <sub>max</sub> (mg/L)	150	
C <sub>min</sub> (mg/L)	1	
Total body clearance (L/h)	1.6-1.8	
T <sub>1/2</sub> (h), mean (range)	4	
AUC <sub>24h</sub> (mg.h/L)	500-800	
Fraction unbound (%)	5	
Volume of distribution (L/kg)	0.11	
Comments	<ul style="list-style-type: none"><li>• 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>• Musson DG, et al. Antimicrob Agents Chemother 2004 48:521</li><li>• Majumdar AK, et al. Antimicrob Agents Chemother 2002 46:3506</li><li>• Laethem T, et al. Antimicrob Agents Chemother 2003 47:1439</li><li>• Merck &amp; Co. <a href="http://www.emea.europa.eu/humandocs/PDFs/EPAR/invanz/H-389-PI-en.pdf">http://www.emea.europa.eu/humandocs/PDFs/EPAR/invanz/H-389-PI-en.pdf</a>. accessed 27-08-2008</li></ul>	

## 5. Pharmacodynamics

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

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

Probabilities of Target Attainment (PTA) for 1000 mg x 1 iv are shown in Figure 1.



**Figure 1. Probabilities of Target Attainment for Ertapenem 1000 mg x 1 IV.**

The following pharmacokinetic parameters were used to obtain the PTA:  
Volume of distribution (Vd): 7.5 L, CV 15%  
Elimination half-life (t): 4 h, CV 15%  
Fraction unbound (Fu): 5 %  
Infusion time 0.5 h

## **7. Clinical data**

Clinical trials have shown the efficacy of ertapenem in treatment of patients with septicaemia, post-operative sepsis, nosocomial pneumonia, community acquired pneumonia, intra-abdominal infections and complicated skin and soft tissue infections caused by micro-organisms categorized as wild type.

## 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% <math>fT &gt; MIC</math>. The 95% confidence interval of the 1000 mg dose administered by 30 min infusion results in an S/I breakpoint of 0.5mg/L.</p> <p>These render wild type Enterobacteriaceae susceptible.</p>
Species-related breakpoints	<p>For <i>Streptococcus pneumoniae</i>, streptococci groups A, B, C, G, other streptococci, <i>Haemophilus</i> spp. and <i>Moraxella catarrhalis</i> breakpoints were set at 0.5/0.5 mg/L as strains with MIC values above 0.5 mg/L are rare or not yet reported.</p> <p>The S/I breakpoint for anaerobes was increased to 1 mg/L to avoid dividing wild type MIC distributions.</p> <p>Susceptibility of staphylococci is inferred from the methicillin susceptibility.</p>
Species without breakpoints	<p><i>Acinetobacter</i> spp., <i>Pseudomonas</i> spp., <i>Enterococcus</i> spp. and <i>Neisseria meningitidis</i> were considered poor targets for ertapenem therapy and for that reason did not receive breakpoints.</p> <p>There was considered to be insufficient evidence to set breakpoints for <i>Neisseria gonorrhoeae</i>.</p>
Clinical qualifications	
Dosage	EUCAST breakpoints apply to ertapenem 1000 mg x 1 daily administered intravenously over 30 minutes as the only dose.
Additional comment	

## **9. Current EUCAST breakpoints**

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

<b>10. Exceptions noted for individual national committees</b>
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