

# Meropenem-vaborbactam: Rationale for EUCAST Clinical Breakpoints

<b>Current version</b>	<b>2.0</b>	<b>January 2024</b>
Previous versions	1.0	February 2021

## Introduction

Meropenem-vaborbactam comprises meropenem, a penem, and vaborbactam, a cyclic boronic acid beta-lactamase inhibitor that protects meropenem from degradation by certain serine beta-lactamases such as *Klebsiella pneumoniae* carbapenemase (KPC). The pharmacokinetics (PK) of vaborbactam, including its distribution in tissues and route of excretion, closely mirror those of meropenem in nonclinical species and in humans.

Meropenem-vaborbactam is active in vitro, in vivo and in clinical studies against *Enterobacterales* including isolates expressing beta-lactamases such as extended-spectrum beta-lactamases (ESBLs) carbapenemases or AmpC beta-lactamases including TEM, SHV, CTX-M, KPC, SME, CMY, and ACT. This version is extracted from version 1.0, and will be the format for future updates. Previous versions are available on request.

Meropenem-vaborbactam is indicated for the treatment of complicated urinary tract infections including pyelonephritis, complicated intra-abdominal infection and hospital-acquired pneumonia, including ventilator associated pneumonia caused by designated susceptible bacteria.

This version is extracted from version 2.0 and will be the format for future updates. Previous versions are available on request.

## Dosages related to clinical breakpoints

**Standard dosage:** meropenem 2 g/vaborbactam 2 g x 3 iv over 3 hours  
**High dosage:** none

## 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

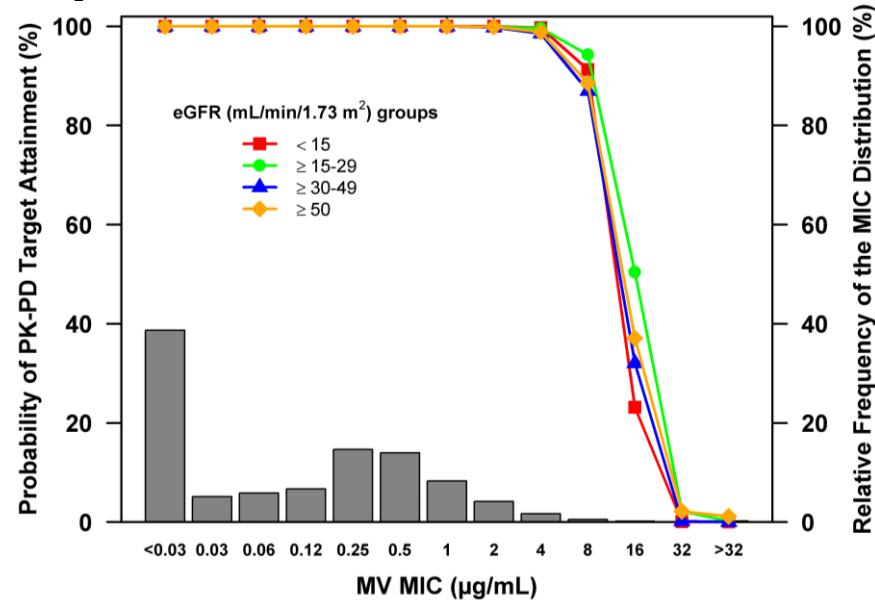
PK parameter	Pharmacological studies		Efficacy studies	
	Meropenem 2g / vaborbactam 2g iv over 3 hours		Meropenem 2g / vaborbactam 2g iv over 3 hours	
C <sub>max</sub> (mg/L), mean (SD)	46.0 (5.7) /	50.7 (8.4)	57.3 (23.0) /	71.3 (28.6)
C <sub>min</sub> (mg/L)				
Total body clearance (L/h) , mean (SD)	14.6 (2.7) /	12.3 (2.2)	10.5 (6.4) /	7.95 (4.3)
T <sub>1/2</sub> (h) , , mean (SD)	1.50 (1.0) /	1.99 (0.8)	2.30 (2.5) /	2.25 (2.1)
AUC <sub>0-8</sub> (mg.h/L) , mean (SD)	38.0 (27.7) /	196.0 (36.7)		
AUC <sub>0-24</sub> (mg.h/L) , mean (SD)	414 /	588 <sup>c</sup>	637 (295) /	821 (369)
AUC <sub>0-∞</sub> (mg.h/L)				
Fraction unbound (%)	98%		67%	
Volume of distribution <sub>ss</sub> (L) , mean (SD)	21.7 (38.2) /	22.0 (41.0)		

## Pharmacodynamics

Index	Neutropenic mouse thigh		<i>In vitro</i> hollow fibre
	<i>Enterobacterales</i>		<i>Enterobacterales</i>
	Meropenem	Vaborbactam	
PK/PD index	f%T>MIC	f24h vaborbactam AUC:meropenem-vaborbactam MIC	f24h vaborbactam AUC:meropenem-vaborbactam MIC
f%T>MIC for bacteriostasis	30	9	12
f%T>MIC for 1-log <sub>10</sub> kill	35	38	18

## Monte Carlo simulations

Percent probabilities of PK/PD target attainment by meropenem-vaborbactam MIC for meropenem-vaborbactam (MV) dosing regimens based on free-drug plasma meropenem %T>MIC targets of 45 and a free-drug vaborbactam AUC:MIC ratio target  $\geq 35$  among simulated patients with cUTI, overlaid upon the meropenem-vaborbactam MIC distribution for 1,331 KPC-producing *Enterobacterales* isolates.



## Clinical studies

Registration of meropenem-vaborbactam was based on two multicentre Phase 3 trials in (1) complicated UTI including pyelonephritis (Tango I, n=545, comparator = piperacillin-tazobactam 5.5 g x 3), and (2) known or suspected carbapenem-resistant *Enterobacterales* (CRE) infections including complicated UTI, acute pyelonephritis, hospital-acquired/ventilator-associated bacterial pneumonia, bacteraemia, or complicated intra-abdominal infection (Tango II, n=43 CRE infections, comparator = best available therapy).

In Tango I, clinical or microbiological failures were uncommon and occurred only with isolates with the lowest MICs suggesting that failures were associated with factors other than the in vitro susceptibility of the baseline isolate.

In Tango II, among patients with CRE infections, meropenem-vaborbactam was associated with higher rates of clinical cure than best available therapy at both end-of-treatment and test-of-cure assessments. The analysis of outcomes demonstrated no obvious cut-off in meropenem-vaborbactam MIC that discriminated between clinical or microbiological successes and failures.

## Clinical breakpoints

The clinical breakpoints for meropenem-vaborbactam can be found in the most recent version of the Breakpoint tables: [https://www.eucast.org/clinical\\_breakpoints](https://www.eucast.org/clinical_breakpoints)

## References

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