

# Cefepime-enmetazobactam: Rationale for EUCAST Clinical Breakpoints

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## Introduction

Cefepime-enmetazobactam comprises cefepime, a cephalosporin, and enmetazobactam, a novel zwitterionic penicillanic acid sulfone beta-lactamase inhibitor that has potent activity against a wide range of extended spectrum beta-lactamases (ESBLs) (including all the most commonly encountered molecular families such as TEM, SHV, and CTX-M variants). The pharmacokinetics of enmetazobactam, including its distribution in tissues and route of excretion, closely mirror those of cefepime in animal models and in humans.

Cefepime-enmetazobactam is active in vitro, in vivo models and in clinical studies against Enterobacterales including isolates expressing beta-lactamases such as ESBLs and other class A beta-lactamases, and AmpC beta-lactamases. In vitro activity of cefepime-enmetazobactam against non-fermenting Gram-negative bacteria such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* is largely similar to that of cefepime alone.

Cefepime-enmetazobactam is licensed for the treatment of the following infections in adults caused by Gram-negative pathogens:

- Complicated urinary tract infection (cUTI), including pyelonephritis.
- Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP).
- Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above
- Treatment of infections due to aerobic gram-negative organisms in adults with limited treatment options.

## Dosages related to clinical breakpoints

**Standard dosage:** 2 g cefepime + 0.5 g enmetazobactam x 3 iv over 2 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
<b>Dosage</b>	<b>Cefepime 2 g and enmetazobactam 1 g iv x 3 over 2 hours Healthy volunteers (n=20)</b>	<b>Cefepime 2 g and enmetazobactam 0.5 g iv over 2 hours, Healthy volunteers (n=102), patients with varying renal function (n=30) plus clinical study subjects (n=531)</b>
C <sub>max</sub> (mg/L)	78.7 (12.2) / 35.5 (5.9)	87.1 (22.1) / 17.4 (5.2)
C <sub>min</sub> (mg/L)		
Total body clearance (L/h)	7.6 (1.5) / 8.2 (1.6)	5.8 (1.6) / 7.7 (2.6)
T <sub>1/2</sub> (h)	2.1 (0.3) / 2.5 (0.6)	2.7 (1.1) / 2.6 (1.1)
AUC <sub>0-8 ss</sub> (mg.h/L)	271.3 (45.8) / 125.7 (20.2)	
AUC <sub>0-24</sub> (mg.h/L)		
AUC <sub>0-∞</sub> (mg.h/L)		364.7 (87.9) / 71.71 (20.9)
Fraction unbound (%)	80% / 100%	
Volume of distribution <sub>ss</sub> (L)	20.1 (3.7) / 20.2 (4.0)	20.6 (5.3) / 25.9 (8.0)

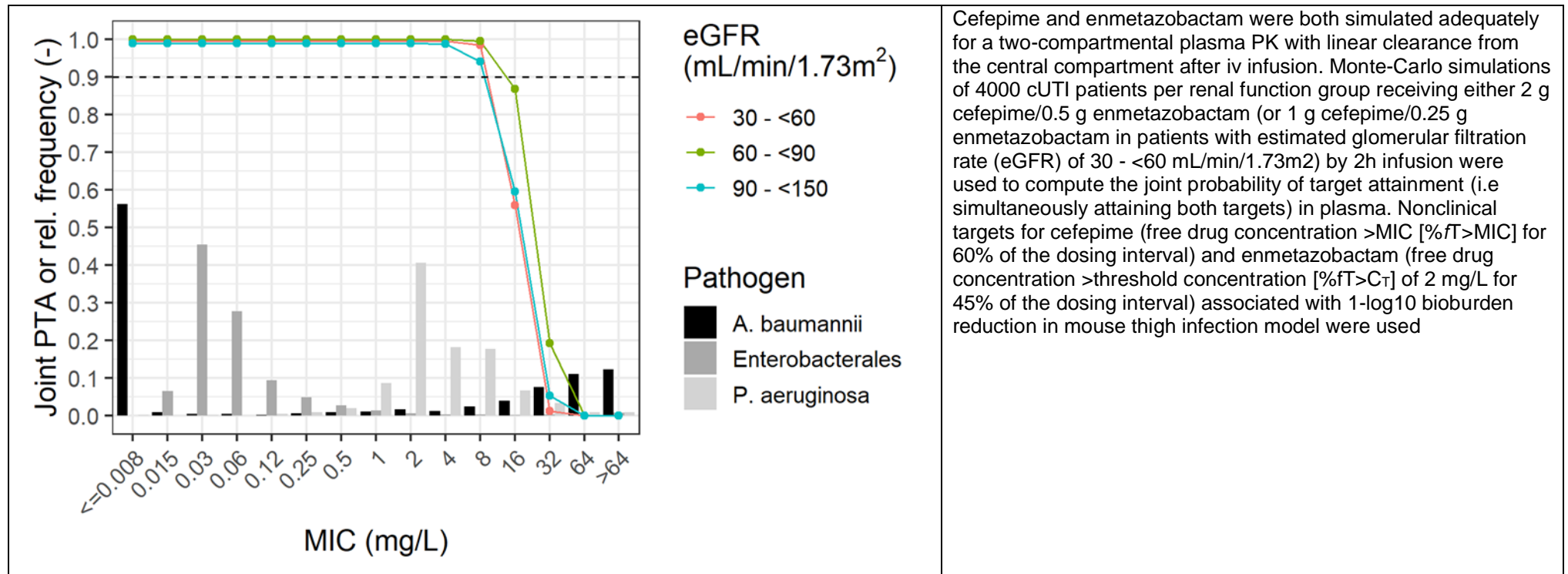
- Values expressed as mean and (SD)

## Pharmacodynamics

	Murine Lung Infection.		Hollow Fibre	Neutropenic Murine Thigh Infection		
	Enterobacterales		Enterobacterales	Enterobacterales		
	Cefepime	Enmetazobactam	Enmetazobactam	Cefepime	Enmetazobactam	
	%fT>MIC	%fT>2 mg/L	%fT>2 mg/L	%fT>MIC	%fT>2 mg/L	
Bacteriostasis			31	40-60	8	
1-log <sub>10</sub> reduction	30		46	40-60	44	
1-log <sub>10</sub> reduction	20	20				

## Monte Carlo simulations

Percent probabilities of PK/PD target attainment by cefepime-enmetazobactam MIC for cefepime-enmetazobactam dosing regimen based on targets of cefepime 60%  $fT > MIC$  and an enmetazobactam 45%  $fT > 2 \text{ mg/L}$  in 4000 simulated patients with cUTI, overlaid upon the cefepime-enmetazobactam MIC distributions for 9,905 Enterobacteriales (which includes 1,007 ESBL producers), 1,165 *P. aeruginosa* and 583 *A. baumannii*.



## Clinical studies

A total of 1041 subjects with a clinical diagnosis of cUTI or AP caused by a Gram-negative urinary pathogen ( $\geq 10^5$  colony-forming units [CFU]/ml in urine) and a clinical severity of illness requiring hospitalization and the use of IV antibiotics for at least 7 days were enrolled. Randomization was in a 1:1 ratio to one of the following groups:

- Cefepime 2 g-enmetazobactam 0.5 mg infused over 2 hours every 8 hours (q8h) for 7 days. In patients with moderate renal impairment (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m<sup>2</sup> and  $\geq 30$  mL/min/1.73 m<sup>2</sup>) the dose of cefepime-enmetazobactam was adjusted to 1 g cefepime plus 250 mg enmetazobactam, infused over a period of 2 hours q8h. In patients with moderate renal impairment at baseline, dose adjustment was applicable from Day 1 of dosing.

- Piperacillin/tazobactam 4.5 g (piperacillin 4 g/tazobactam 0.5 g) infused over 2 hours q8h for 7 days. Dosing of piperacillin/tazobactam followed the recommendations as per the respective summary of product characteristics, which did not require adjustment of the 4.5 g dose in patients with mild or moderate renal impairment.

Patients with severe renal impairment (eGFR <30 mL/min/1.73 m<sup>2</sup>) were excluded from study participation. At the discretion of the Investigator, treatment may have continued for up to 14 days in subjects with a positive blood culture at baseline. No switch to oral antibiotic therapy was permitted.

Demographics, baseline disease characteristics, and underlying comorbidities were similar in the cefepime-enmetazobactam and piperacillin/tazobactam groups in Study AT-301 and were also consistent with a seriously ill population requiring hospitalization and IV antibiotic for treatment of cUTI/AP. The five most common baseline uropathogens were *E. coli*, *K. pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Enterobacter cloacae*.

Overall success was seen in a higher proportion of subjects at the primary efficacy endpoint in the cefepime-enmetazobactam group compared with the piperacillin/tazobactam group (79.1% vs 58.9%), with a treatment difference of 21.2% (95% CI: 14.3%, 27.9%). Because the lower limit of the 95% CI is greater than the prespecified noninferiority margin of -10%, cefepime-enmetazobactam is noninferior to piperacillin/tazobactam. Additionally, because the lower limit of the 95% CI of the difference is also greater than 0%, cefepime-enmetazobactam met criteria for superiority to piperacillin/tazobactam.

#### Outcomes by MIC Enterobacterales

MIC (mg/L)	≤0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	>64
<b>N</b>	3	28	188	88	26	8	4	4	3	-	-	2	1	-	2
<b>Microbiological eradication</b>	3	25	170	70	17	4	4	4	3	-	-	2	0	-	1
<b>%</b>	100	89.3	90.4	79.5	65.4	50	100	100	100	-	-	100	0	-	50
<b>Clinical cure</b>	3	26	178	80	21	7	4	4	3	-	-	2	0	-	2
<b>%</b>	100	92.9	94.7	90.9	80.8	87.5	100	100	100	-	-	100	0	-	100
<b>Overall success</b>	3	23	166	65	15	4	4	4	3	-	-	2	0	-	1
<b>%</b>	100	82.1	88.3	73.9	57.7	50	100	100	100	-	-	100	0	-	50

#### Outcomes by MIC *Pseudomonas aeruginosa*

MIC (mg/L)	1	2	4	8	16	32	64	>64
<b>N</b>	1	3	5	6	-	3	-	2
<b>Microbiological eradication</b>	0	1	2	3	-	3	-	1
<b>%</b>	0	33.3	40.0	50.0	-	100	-	50
<b>Clinical cure</b>	1	3	5	5	-	3	-	2
<b>%</b>	100	100	100	83.3	-	100	-	100

<b>Overall success</b>	0	1	2	3	-	3	-	1
<b>%</b>	0	33.3	40.0	50.0	-	100	-	50

## Clinical breakpoints

The clinical breakpoints for cefepime-enmetazobactam 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

- Muller AE, Attwood M, Van den Berg S, Chavan R, Periasamy H, Noel A, MacGowan A. Cefepime pharmacodynamic targets against Enterobacterales employing neutropenic murine lung infection and in vitro pharmacokinetic models. *J Antimicrob Chemother.* 2022; 77:3504-3509.
- Bernhard F, Odedra R, Sordello S, Cardin R, Franzoni S, Charrier C, Belley A, Warn P, Machacek M, Knechtle P. Pharmacokinetics-Pharmacodynamics of Enmetazobactam Combined with Cefepime in a Neutropenic Murine Thigh Infection Model. *Antimicrob Agents Chemother.* 2020; 64:e00078-20.
- Johnson A, McEntee L, Farrington N, Kolamunnage-Dona R, Franzoni S, Vezzelli A, Massimiliano M, Knechtle P, Belley A, Dane A, Drusano G, Das S, Hope W. Antimicrob Agents Chemother. Pharmacodynamics of Cefepime Combined with the Novel Extended-Spectrum-beta-Lactamase (ESBL) Inhibitor Enmetazobactam for Murine Pneumonia Caused by ESBL-Producing *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 2020; 64:e00180-20.