

Imipenem-relebactam: Rationale for EUCAST Clinical Breakpoints

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Previous version	2.0	January 2024

Introduction

Relebactam (REL; also known as MK-7655) is a small-molecule diazabicyclooctane beta-lactamase inhibitor (BLI) with sub-micromolar potency for AmpC, a class C beta-lactamase responsible for resistance in a majority of imipenem-resistant *Pseudomonas aeruginosa*. In addition, REL is active against the class A *Klebsiella pneumoniae* carbapenemase (KPC) β -lactamase present in some Enterobacterales, including *Klebsiella* strains, as well as against many other class A and C beta-lactamases.

Imipenem is a carbapenem with activity against a broad spectrum of clinical isolates including Enterobacterales and *P. aeruginosa*, though resistance has developed since its introduction in 1985. Resistance to imipenem in *P. aeruginosa* depends on both production of the chromosomally-encoded class C AmpC enzyme carried by virtually all isolates, as well as loss of the imipenem entry porin OprD. Enterobacterales expressing various class A and class C enzymes including extended spectrum beta-lactamases (ESBL) generally remain susceptible to carbapenems, except when two entry porins are lost (OmpC and OmpF, or the equivalent).

This version is extracted 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: Imipenem/cilastatin/relebactam 500 mg/500 mg/250 mg x 4 iv, over 30 minutes
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	
	Imipenem 500 mg	Relebactam 250 mg		
Dosage				
C _{max} (mg/L) (SD)	31.7 (27)	16.8 (25)		
C _{min} (mg/L) (SD)	0.60 (34)	0.87 (31)		
Total body clearance (L/h) (SD)	12.0 (18)	8.8 (18)		
T _{1/2} (h), mean (range) (SD)	1.1 (12)	1.7 (14)		
AUC ₀₋₁₂ (mg.h/L)				
AUC ₀₋₂₄ (mg.h/L) (SD)	41.3 (18)	28.4 (18)		
AUC _{0-∞} (mg.h/L)				
Fraction unbound (%)	80	78		
Volume of distribution _{ss} (L)	15.8	17.4		

Pharmacodynamics

Index	Neutropenic Mouse Thigh (Mavridou et al., 2015)		Hollow Fibre (Bhagunde et al., 2019)	Hollow Fibre (MacGowan 2025)
	<i>P. aeruginosa</i>	<i>K. pneumoniae</i>	<i>P. aeruginosa</i>	<i>P. aeruginosa</i>
	n = 5	n = 2	n = 5	n = 8
Relebactam <i>f</i> AUC for bacteriostasis	6.3 - 40.3	6.4 - 45.2		
Relebactam <i>f</i> AUC/MIC for bacteriostasis			2.7	
Relebactam <i>f</i> AUC/MIC for 1- and 2-log ₁₀ drop				
Imipenem <i>f</i> %T>MIC for bacteriostasis in combination with relebactam	0 - 22.4	0 - 34.1		30.5
Imipenem <i>f</i> %T>MIC for 1 and 2log ₁₀ drop in combination with relebactam			4.7 and 7.5	32.9 and 34.2

Monte Carlo simulations

Simulations based on conventional (imipenem – 2 log₁₀ kill) and model targets mouse thigh (relebactam - stasis)

Percentage of Patients Achieving 40% of $fT > MIC$ for Imipenem and $fAUC/MIC=7.5$ for Relebactam at Steady State

CrCL	Percentage of Patients Achieving 40% of $fT > MIC$ for Imipenem and $fAUC/MIC=7.5$ for Relebactam												
	MIC (mg/mL)	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64
<15 mL/min (ESRD)		100	100	100	100	100	100	99.6	90.3	48.4	10.1	0.5	0
15 - 30 mL/min (SRI)		100	100	100	100	100	100	97.3	71.2	24.2	1.4	0	0
30 - 60 mL/min (MRI)		100	100	100	100	100	100	96.8	73.3	26.4	1.8	0.1	0
60 - 90 mL/min (MIRI)		100	100	100	100	100	99.9	96.0	74.0	25.5	2.0	0	0
90 - 150 mL/min (NRF)		100	100	100	100	100	99.5	93.5	66.9	23.0	1.5	0	0
150 – 180 mL/min (ARF)		100	100	100	100	100	98.4	87.9	49.3	11.0	0.3	0	0
180 – 210 mL/min (ARF)		100	100	100	100	99.7	97.1	83.1	41.3	7.1	0.1	0	0
210 - 250 mL/min (ARF)		100	100	100	100	99.5	95.2	76.9	33.1	4.3	0	0	0

ESRD: End Stage Renal Disease, SRI: Severe Renal Impairment, MRI: Moderate Renal Impairment, MIRI: Mild Renal Impairment, NRF: Normal Renal Function; ARF: Augmented Renal Function

Clinical studies

Imipenem-relebactam has been studied in two Phase 2 clinical trials in subjects with complicated UTI (PN003, two different doses of relebactam, n=213, comparator = imipenem alone) and complicated intra-abdominal infection (PN004, two different doses of relebactam, n=250, comparator = imipenem alone) and in a Phase 3 clinical trial in subjects with infections caused by imipenem-nonsusceptible pathogens (PN013). No clear relationship between MIC and clinical or microbiological outcome was observed when data from the three studies were pooled.

Clinical breakpoints

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

References

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