

Aztreonam-avibactam: Rationale for EUCAST Clinical Breakpoints

Current version	1.0	July 2024
------------------------	------------	------------------

Introduction

Avibactam is a diazabicyclooctane non- β -lactam β -lactamase inhibitor that protects the antimicrobial activity of aztreonam when used in combination. Avibactam differs from other clinically used β -lactamase inhibitors, such as clavulanic acid, sulbactam, and tazobactam, in several key aspects, such as chemical structure, expanded spectrum of β -lactamase inhibition, and covalent reversible mechanism of inhibition. Avibactam inhibits both Ambler class A and class C β -lactamases and some class D enzymes, including extended-spectrum β -lactamases (ESBLs), *Klebsiella pneumoniae* carbapenemase (KPC) and OXA-48 carbapenemases, and AmpC enzymes.

Aztreonam-avibactam is licensed for the treatment of the following infections in adults: complicated intra-abdominal infection (cIAI), hospital-acquired pneumonia (HAP), ventilator associated pneumonia (VAP), and complicated urinary tract infection (cUTI), including pyelonephritis. Aztreonam-avibactam is also indicated for the treatment of infections due to aerobic Gram-negative bacteria in adult patients for which there are limited treatment options

Dosages related to clinical breakpoints

Standard dosage: Loading dose 2 g aztreonam + 0.67 g avibactam iv over 3 hours
Maintenance doses 1.5 g aztreonam/0.5 g avibactam x 4 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	
Dosage	1.5 g aztreonam/0.5 g avibactam q6h (iv 3-h infusion); healthy volunteers (N=6) Geometric mean (CV%)	1.5 g aztreonam/0.5 g avibactam q6h (iv 3-h infusion); cIAI patients (N=97) Geometric mean (CV%)	1.5 g aztreonam/0.5 g avibactam q6h (iv 3-h infusion); HAP/VAP patients (N=28) Geometric mean (CV%)
C _{max} (mg/L)	57.34 (13) / 11.08 (14)	51.12 (42.02) / 10.47 (46.73)	63.72 (27.06) / 12.73 (29.47)
C _{min} (mg/L)	21.43 (19) / 3.1 (24)		
Total body clearance (L/h)	6.5 (16) / 12.16 (18)	7.1 (44.97) / 12.27 (47.86)	5.56 (29.43) / 9.87 (30.27)
T _{1/2} (h), mean (SD)	2.605 (0.349) / 3.188 (0.071)		
AUC ₀₋₂₄ ss (mg.h/L)	922.9 (16) / 164.8 (18)	775.73 (47.24) / 151.75 (49.6)	1022.2 (27.74) / 193.62 (28.39)
AUC ₀₋₆ ss (mg.h/L)	230.8 (16) / 41.19 (18)		
AUC _{0-∞} (mg.h/L)			
Fraction unbound (%)	62% / 92%		
Volume of distribution _{ss} (L)	23.70 (29) / 37.37 (30)		

- Pfizer data on file

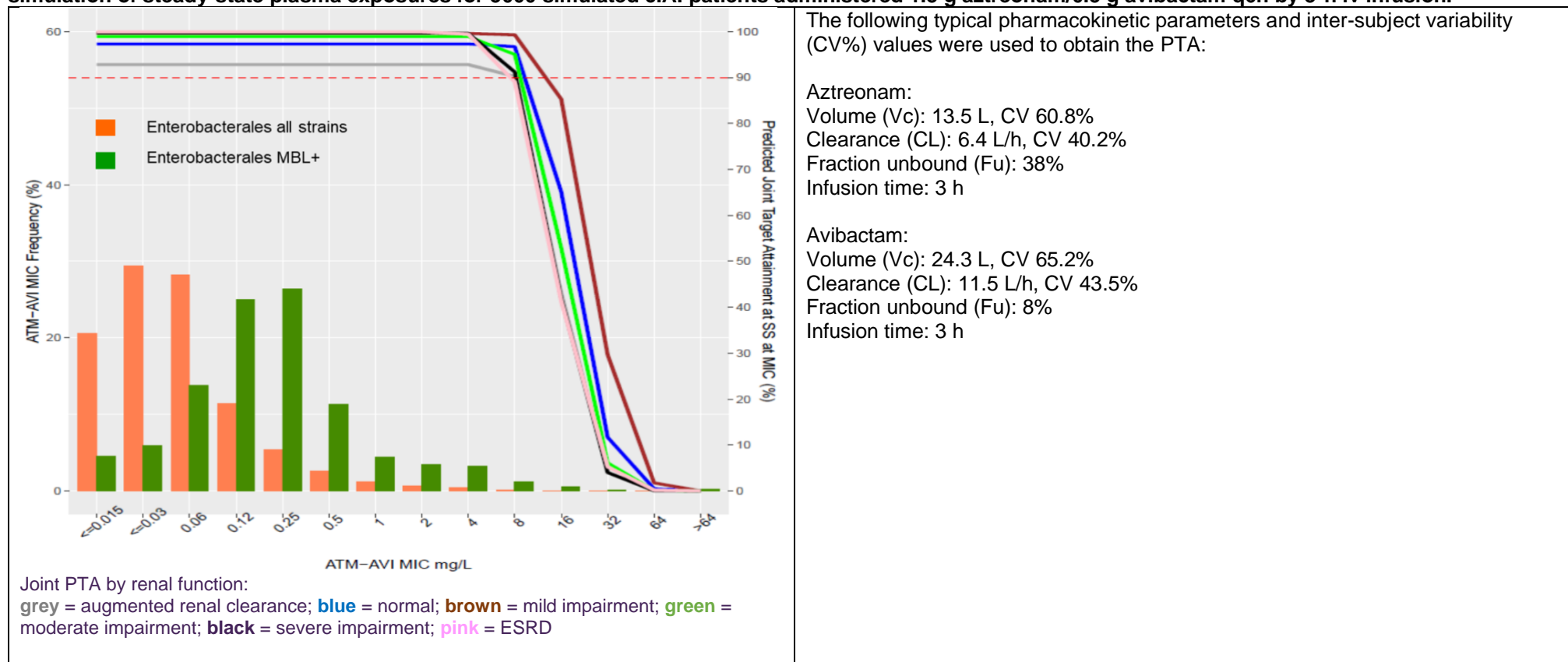
Pharmacodynamics

Index	In vitro Hollow Fibre ^{1,2}		Index	Neutropenic Mouse Thigh ^{1,2}		Neutropenic Mouse Lung	
	Enterobacterales			Enterobacterales		Enterobacterales	
	Aztreonam	Avibactam		Avibactam		Avibactam	
f%T>MIC (aztreonam), f%T>C _T of 2.5 (avibactam) mg/L for stasis		36.1-56.4	f%T>C _T of 2.5 (avibactam) mg/L for bacteriostasis	23			
f%T>MIC (aztreonam), f%T>C _T of 2.5 (avibactam) mg/L for 1-log ₁₀ kill	50-55	40.9-58.2	f%T>C _T of 2.5 (avibactam) mg/L for 1-log ₁₀ kill	35-40		<1-20	

- Six aztreonam-resistant Enterobacterales isolates (three *K. pneumoniae* and three *Escherichia coli*) all coproducing an MBL and an ESBL and/or a class C β-lactamase (CMY type) were used in these experiments. The MIC values of aztreonam-avibactam against these isolates ranged from 0.125 to 8 mg/L

Monte Carlo simulations

Probabilities of target attainment (PTA) for the joint PK/PD target (60% $fT > MIC_{ATM-AVI}$ for ATM and 50% $fT > CT$ of 2.5 mg/L for AVI) determined by Monte Carlo simulation of steady-state plasma exposures for 5000 simulated cIAI patients administered 1.5 g aztreonam/0.5 g avibactam q6h by 3-h iv infusion.



Clinical studies

REVISIT was a phase 3, prospective, randomized, multicentre, open-label, central assessor-blinded study in hospitalized adults. Patients were randomized 2:1 to ATM-AVI (\pm metronidazole [MTZ]; cIAI patients only) or meropenem (MER) \pm colistin (COL) for 5–14 (cIAI) or 7–14 (HAP/VAP) days. Clinical cure at the test-of-cure (TOC) visit in the intent-to-treat (ITT) and clinically evaluable (CE) analysis sets were the primary efficacy endpoints. Key secondary endpoints included microbiological responses at TOC, 28-day mortality, and safety (presented at ID Week, Late Breaker abstract #1605428, October 14, 2023).

Table 1. Adjudicated clinical response at the TOC visit (ITT and CE analysis sets)

	cIAI		HAP/VAP		Overall	
ITT analysis set	ATM-AVI + MTZ (n=208)	MER ± COL (n=104)	ATM-AVI (n=74)	MER ± COL (n=36)	ATM-AVI ± MTZ (n=282)	MER ± COL (n=140)
Cure, n (%) [95%CI]	159 (76.4) [70.3, 81.8]	77 (74.0) [65.0, 81.7]	34 (45.9) [34.9, 57.3]	15 (41.7) [26.7, 57.9]	193 (68.4) [62.8, 73.7]	92 (65.7) [57.6, 73.2]
Difference, % (95% CI)	2.4 (-12.4, 19.1)		4.3 (-25.6, 32.2)		2.7 (-11.4, 17.8)	
CE analysis set	ATM-AVI + MTZ (n=168)	MER ± COL (n=83)	ATM-AVI (n=45)	MER ± COL (n=22)	ATM-AVI ± MTZ (n=213)	MER ± COL (n=105)
Cure, n (%) [95%CI]	143 (85.1) [79.2, 89.9]	66 (79.5) [69.9, 87.1]	21 (46.7) [32.7, 61.1]	12 (54.5) [34.3, 73.7]	164 (77.0) [71.0, 82.3]	78 (74.3) [65.3, 81.9]
Difference, % (95% CI)	5.6 (-8.9, 23.1)		-7.9 (-42.8, 29.4)		2.7 (-11.9, 19.2)	

ATM-AVI, aztreonam-avibactam; CE, clinically evaluable; CI, confidence interval; cIAI, complicated intra-abdominal infection; COL, colistin; HAP, hospital-acquired pneumonia; ITT, intent-to-treat; MER, meropenem; MTZ, metronidazole; TOC, test-of-cure; VAP, ventilator-acquired pneumonia.

Single arm CIs were computed using Jeffrey's method.

Clinical breakpoints

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

References

1. Singh R, Kim A, Tanudra MA, et al. Pharmacokinetics/pharmacodynamics of a beta-lactam and beta-lactamase inhibitor combination: a novel approach for aztreonam/avibactam. *J Antimicrob Chemother.* 2015;70(9):2618-26.
2. Nichols WW, Newell P, Critchley IA, Riccobene T, Das S. Avibactam pharmacokinetic/pharmacodynamic targets. *Antimicrob Agents Chemother* 2018;62(6): e02446-17.