In vitro activity of sulopenem and comparator agents against U.S. Enterobacterales clinical isolates, SENTRY antimicrobial surveillance program, 2023

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ABSTRACT

Background
Sulopenem is a thiopenem antibacterial with an oral and parenteral formulation. Sulopenem etzadroxil/probenecid, the oral formulation, was recently approved by the US FDA for the treatment of women with uncomplicated urinary tract infection. This study evaluated the in vitro activity of sulopenem and comparator agents against contemporary Enterobacterales clinical isolates predominantly from patients with urinary tract infections.
Methods
A contemporary collection of 1,086 community- and nosocomial-acquired Enterobacterales isolates was assembled from US medical centers. Isolates were susceptibility tested using the CLSI broth microdilution reference method.
Results
Sulopenem demonstrated potent in vitro antimicrobial activity ($MIC_{50/90}$, 0.03/0.25 mg/L) against Enterobacterales isolates regardless of infection type, inhibiting 98.0% of isolates at ≤0.5 mg/L. This activity was conserved against resistant phenotypes including ESBL-phenotype *Escherichia coli* ($MIC_{50/90}$, 0.03/0.06 mg/L) and ESBL-phenotype *Klebsiella pneumoniae* ($MIC_{50/90}$, 0.06/0.12 mg/L). Sulopenem maintained activity against ciprofloxacin-, nitrofurantoin- and trimethoprim/sulfamethoxazole-non-susceptible subsets, including urinary isolates from patients in the community ($MIC_{50/90}$, 0.03-0.12/0.12-0.5 mg/L). Sulopenem also maintained activity against community-acquired ESBL-producing Enterobacterales urinary isolates non-susceptible to two or more oral antimicrobial agents commonly used to treat urinary tract infections.
Conclusion
The potent in vitro activity of sulopenem against this large collection of contemporary Enterobacterales clinical isolates from multiple infection types supports its use in the treatment of uncomplicated urinary tract infection, as well as its further clinical evaluation in the treatment of other common bacterial infections demonstrating resistant phenotypes.

Table. Antimicrobial activity of sulopenem against Enterobacterales urinary isolates non-susceptible to oral antimicrobial agents commonly used to treat UTI

Source	Resistant antibiotic(s) (MIC), N	Sulopenem $MIC_{50/90}$ (mg/L)	Sulopenem MIC ≤0.5 mg/L (S/I), n(%)	Sulopenem MIC ≥1 mg/L (R), n(%)
Community-acquired urinary isolates, N=507	Ciprofloxacin (MIC ≥1 ng/L), N=47	0.03/0.12	47 (100.0)	0 (0.0)
	TMP-SMX (MIC ≥4/76 mg/L), N=129	0.03/0.12	129 (100.0)	0 (0.0)
	Nitrofurantoin (MIC >64 mg/L), N=53	0.12/0.5	49 (92.5)	4 (7.5)
	ESBL phenotype (CTX MIC ≥4 mg/L), N=55	0.03/0.12	55 (100.0)	0 (0.0)
	Ciprofloxacin and ESBL phenotype, N=20	0.03/0.06	20 (100.0)	0 (0.0)
	Ciprofloxacin, TMP-SMX and ESBL phenotype, N=15	0.03/0.12	15 (100.0)	0 (0.0)
	Ciprofloxacin, TMP-SMX, nitrofurantoin and ESBL phenotype, N=6	--/--	6 (100.0)	0 (0.0)
All urinary isolates, N=728	Ciprofloxacin (MIC ≥1 ng/L), N=74	0.03/0.25	73 (98.6)	1 (1.4)
	TMP-SMX (MIC ≥4/76 mg/L), N=173	0.03/0.12	171 (98.8)	2 (1.2)
	Nitrofurantoin (MIC >64 mg/L), N=87	0.12/0.5	80 (92.0)	7 (8.0)
	ESBL phenotype (CTX MIC ≥4 mg/L), N=90	0.03/0.25	88 (97.8)	2 (2.2)
	Ciprofloxacin and ESBL phenotype, N=32	0.03/0.12	31 (96.9)	1 (3.1)
	Ciprofloxacin, TMP-SMX and ESBL phenotype, N=25	0.03/0.5	24 (96.0)	1 (4.0)
	Ciprofloxacin, TMP-SMX, nitrofurantoin and ESBL phenotype, N=7	--/--	7 (100.0)	0 (0.0)

INTRODUCTION

The continued emergence and spread of antibacterial resistance have made it very challenging to choose empiric therapy for patients with acute infectious diseases. When choosing empiric therapy, prescribers must consider the treatment setting and evaluate the patient in terms of severity of illness and a variety of host factors. Sulopenem is a broad-spectrum, synthetic, thiopenem β-lactam antibiotic that uniquely possesses both oral and parenteral formulations. Other FDA-approved carbapenem antibiotics are only available in their parenteral formulation, requiring hospitalization or outpatient infusion services for their administration. Sulopenem has activity against both Gram-positive and Gram-negative pathogens, including fluoroquinolone-resistant, ESBL-producing, and multidrug resistant Enterobacterales. Sulopenem etzadroxil/probenecid (ORLYNVAH™), the oral formulation, was approved by the US FDA in October 2024 for the treatment of women with uncomplicated urinary tract infection (uUTI). This study evaluated the in vitro activity of sulopenem and comparator agents against contemporary Enterobacterales clinical isolates predominantly from patients with urinary tract infections in the United States (2023).

METHODS

A total of 1,086 Enterobacterales isolates were collected in 2023 from 52 centers representing all 9 US Census Divisions as part of the SENTRY Antimicrobial Surveillance Program [Element Iowa City, JMI Laboratories]. Enterobacterales isolates were collected from patients with urinary tract infection, bloodstream infection (BSI) and intraabdominal infection (IAI). Analysis included evaluations of resistant subsets for most pathogen groups. Carbapenem-resistant Enterobacterales (CRE) and extended-spectrum β-lactamase (ESBL)-phenotype definitions were applied to Enterobacterales isolates using Clinical and Laboratory Standards Institute (CLSI) breakpoint criteria. Bacterial species were identified by the submitting laboratories and confirmed by Element Iowa City using standard microbiology methods and matrix-assisted laser desorption ionization-time of flight mass spectrometry [Bruker Daltonics, Bremen, Germany]. Enterobacterales isolates were tested for antimicrobial susceptibility using reference broth microdilution methods with frozen-form 96-well broth microdilution panels. The testing medium was cation-adjusted Mueller-Hinton broth. Concurrent quality assurance testing for Enterobacterales isolates utilized CLSI-recommended quality control reference strains, including *Enterococcus faecalis* ATCC 29212, *E. coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, and *Staphylococcus aureus* ATCC 29213. Concurrent bacterial colony counts monitored inoculum density throughout susceptibility testing. CLSI, European Committee on Antimicrobial Susceptibility Testing (EUCAST), and United States Food and Drug Administration (US-FDA) breakpoint criteria were utilized to determine susceptibility and resistance rates for comparator agents, where available.

RESULTS

The 1,086 Enterobacterales isolates consisted of 635 *Escherichia coli*, 217 *Klebsiella* spp., 70 *Proteus mirabilis*, 48 *Enterobacter cloacae* species complex, and 116 other Enterobacterales species. These isolates were recovered from patients with UTI (67.0%; n=728), BSI (25.0%; n=272) and IAI (8.0%; n = 86). The activity of sulopenem was the same as for imipenem but lower than for meropenem (Table 1). Sulopenem demonstrated potent in vitro antibacterial activity ($MIC_{50/90}$, 0.03/0.25mg/L; 92.9% susceptible) regardless of infection type, inhibiting 98.0% of all Enterobacterales isolates at ≤0.5 mg/L, which is within the CLSI susceptible MIC breakpoint criteria for parenteral carbapenems against Enterobacterales and within the FDA MIC breakpoints for sulopenem (Table 2). For the subset of 728 Enterobacterales urinary isolates, including both community-acquired and nosocomial strains, sulopenem exhibited potent in vitro activity ($MIC_{50/90}$, 0.03/0.25 mg/L) (Table 3). Notably, sulopenem maintained potent in vitro antibacterial activity against community-acquired ESBL-producing Enterobacterales and to Enterobacterales urinary isolates non-susceptible (NS) to oral antimicrobial agents commonly used to treat uUTI. Sulopenem exhibited potent in vitro antibacterial activity against community-acquired ESBL-phenotype Enterobacterales urinary isolates, including multidrug resistant isolates NS to three or more oral antimicrobial agents commonly used to treat uUTI (Table 4).

Table 1: Antimicrobial activity of sulopenem and comparator agents tested against 1086 Enterobacterales isolates

Antimicrobial agent	No. of isolates	mg/L			CLSI[a]			EUCAST[a]			US FDA[a]		
		MIC_{50}	MIC_{90}	MIC range	%S	%I	%R	%S	%I	%R	%S	%I	%R
Sulopenem	1,086	0.03	0.25	≤0.008 to >16							92.9	5.1	2.0
Imipenem	1,086	≤0.12	1	≤0.12 to >8	92.9	5.4	1.7	98.3	1.5	0.2	92.9 [b]	5.4	1.7
Meropenem	1,086	≤0.01	0.06	≤0.015 to >32	99.7	0.0	0.3	99.7 [c]		0.3	99.7 [b]	0.0	0.3
		5						99.7 [d]	0.1	0.2			
Amikacin	1,086	2	4	≤0.25 to 32	96.3	2.9	0.8	99.2 [e]		0.8	99.7	0.3	0.0
Amoxicillin-clavulanate	639	4	>32	0.5 to >32	74.2	10.0	15.8				74.2 [b]	10.0	15.8
Aztreonam	1,084	0.12	16	≤0.03 to >16	87.1	1.6	11.3	83.3	3.8	12.9	87.1 [b]	1.6	11.3
Cefepime	1,086	0.06	4	≤0.03 to >32	89.9 [f]	3.4	6.7	87.8	3.6	8.6	89.9	3.4	6.7
Ceftazidime	1,086	0.25	8	0.03 to >32	87.9	2.2	9.9	84.3	3.7	12.1	87.9 [b]	2.2	9.9
Ceftriaxone	1,086	≤0.06	>8	≤0.06 to >8	83.0	1.6	15.5	83.0 [c]		17.0	83.0 [b]	1.6	15.5
								83.0 [d]	1.6	15.5			
Cefuroxime	639	4	>32	≤0.5 to >32	67.8 [g]	12.8	19.4				77.9		22.1
					77.9 [h]	2.7	19.4				67.8 [g,b]	12.8	19.4
Ciprofloxacin	639	0.015	>4	≤0.008 to >4	79.8	2.0	18.2	76.7 [c]		23.3	79.8 [b]	2.0	18.2
								79.8 [d]	2.0	18.2			
Gentamicin	1,086	0.5	2	≤0.12 to >16	90.4	0.4	9.2	90.4 [e]		9.6	90.8	0.7	8.5
Levofloxacin	1,086	0.06	8	≤0.015 to >32	82.4	1.6	16.0	82.4	1.6	16.0	82.4 [b]	1.6	16.0
Nitrofurantoin	639	16	>64	≤4 to >64	67.3 [i]	12.1	20.7				67.3 [b]	12.1	20.7
Piperacillin-tazobactam	1,086	2	8	≤0.06 to >128	93.6	2.4	4.1	93.6		6.4	95.9	2.0	2.0
Tetracycline	639	1	>16	0.5 to >16	72.8	0.6	26.6				72.8 [b]	0.6	26.6
Tigecycline	1,086	0.25	1	≤0.06 to 8							97.8	2.1	0.1
TMP-SMX	1,086	≤0.12	>4	≤0.12 to >4	76.6		23.4	76.6	1.0	22.4	76.6 [b]		23.4

[a] Criteria as published by CLSI (2023), EUCAST (2023), and US FDA (2023); US FDA breakpoint criteria for sulopenem were applied to all Enterobacterales isolates for comparison purposes.

[b] CLSI M100 standard is recognized.
[c] Using meningitis breakpoints.
[d] Using non-meningitis breakpoints.
[e] For infections originating from the urinary tract. For systemic infections, aminoglycosides must be used in combination with other active therapy.
[f] Intermediate is interpreted as susceptible-dose dependent.
[g] Using oral breakpoints.
[h] Using parenteral breakpoints.
[i] Using UTI only breakpoints.
Organisms include Citrobacter amalonaticus (1), C. amalonaticus/farmeri (2), C. freundii (2), C. freundii species complex (26), C. koseri (20), Enterobacter cloacae species complex (48), Escherichia coli (635), E. hermannii (1), Hafnia alvei (1), Klebsiella aerogenes (22), K. oxytoca (31), K. pneumoniae (163), K. variicola (1), Morganella morganii (13), Phytobacter diazotrophicus (1), Proteus hauseri (1), P. mirabilis (70), P. vulgaris (1), P. vulgaris group (4), Providencia rettgeri (5), P. stuartii (4), Serratia marcescens (29), unspeciated Pantoea (1), and unspeciated Raoultella (4).

Table 2: FDA antibacterial susceptibility test interpretive criteria for sulopenem etzadroxil plus probenecid

	Minimum Inhibitory Concentrations (mg/L)		
Pathogen	S	I	R
Enterobacterales [a]	≤ 0.25	0.5	≥ 1.0

S = susceptible; I = intermediate; R = resistant
[a] Clinical efficacy was shown for *E. coli*, *K. pneumoniae*, and *P. mirabilis*.

Table 3: Antimicrobial activity of sulopenem tested against main organisms / groups originating from urinary tract infections

Organism/organism group (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of:													MIC_{50}	MIC_{90}
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>[a]		
Enterobacterales (728)	0	112	402	99	36	42	26	7	1	2	0	0	1	0.03	0.25
	0.0	15.4	70.6	84.2	89.1	94.9	98.5	99.5	99.6	99.9	99.9	99.9	100.0		
Carbapenem-resistant (CRE) (1)												0	1		
												0.0	100.0		
Escherichia coli (456)	0	104	308	35	4	2	2	0	0	0	0	0	1		
	0.0	22.8	90.4	98.0	98.9	99.3	99.8	99.8	99.8	99.8	99.8	99.8	100.0	0.03	0.03
Non-ESBL-phenotype (387)	0	100	262	20	4	1									
	0.0	25.8	93.5	98.7	99.7	100.0								0.03	0.03
ESBL-phenotype (69)	0	4	46	15	0	1	2	0	0	0	0	0	1		
	0.0	5.8	72.5	94.2	94.2	95.7	98.6	98.6	98.6	98.6	98.6	98.6	100.0	0.03	0.06
Meropenem-susceptible (≤1 mg/L) (455)	0	104	308	35	4	2									
	0.0	22.9	90.5	98.2	99.1	99.6	100.0							0.03	0.03
Meropenem-nonsusceptible (>1 mg/L) (1)												0	1		
												0.0	100.0		
Klebsiella spp. (129)	0	3	64	48	10	3	1								
	0.0	2.3	51.9	89.1	96.9	99.2	100.0							0.03	0.12
Klebsiella pneumoniae (97)	0	2	51	39	4	1									
	0.0	2.1	54.6	94.8	99.0	100.0								0.03	0.06
Non-ESBL-phenotype (85)	0	2	48	31	4										
	0.0	2.4	58.8	95.3	100.0									0.03	0.06
ESBL-phenotype (12)		0	3	8	0	1									
		0.0	25.0	91.7	91.7	100.0								0.06	0.06
Meropenem-susceptible (≤1 mg/L) (97)	0	2	51	39	4	1									
	0.0	2.1	54.6	94.8	99.0	100.0								0.03	0.06
Klebsiella oxytoca (20)	0	1	13	6											
	0.0	5.0	70.0	100.0										0.03	0.06
Klebsiella aerogenes (12)			0	3	6	2	1								
			0.0	25.0	75.0	91.7	100.0							0.12	0.25
Proteus mirabilis (48)				0	4	27	16	1							
				0.0	8.3	64.6	97.9	100.0						0.25	0.5
Non-ESBL-phenotype (47)				0	3	27	16	1							
				0.0	6.4	63.8	97.9	100.0						0.25	0.5
ESBL-phenotype (1)				0	1										
				0.0	100.0										
Enterobacter cloacae species complex (19)		0	3	5	7	3	1								
		0.0	15.8	42.1	78.9	94.7	100.0							0.12	0.25
Ceftazidime-susceptible (≤4 mg/L) (13)		0	2	4	6	0	1								
		0.0	15.4	46.2	92.3	92.3	100.0							0.12	0.12
Ceftazidime-nonsusceptible (>4 mg/L) (6)		0	1	1	1	3									
		0.0	16.7	33.3	50.0	100.0								0.12	
Morganella morganii (7)					0	3	3	1							
					0.0	42.9	85.7	100.0						1	
Citrobacter koseri (19)	0	4	13	1	1										
	0.0	21.1	89.5	94.7	100.0									0.03	0.06
Citrobacter freundii species complex (21)	0	1	9	8	3										
	0.0	4.8	47.6	85.7	100.0									0.06	0.12
Serratia marcescens (9)				0	2	2	3	0	2						
				0.0	22.2	44.4	77.8	77.8	100.0					1	
Proteus vulgaris group (5)		0	1	0	1	2	1								
		0.0	20.0	20.0	40.0	80.0	100.0							0.25	
Providencia spp. (7)				0	5	2									
				0.0	71.4	100.0								0.12	
Other Enterobacterales (8)		0	4	2	1	1									
		0.0	50.0	75.0	87.5	100.0								0.03	

[a] Greater than the highest concentration tested.

US FDA breakpoint criteria for sulopenem were applied to all Enterobacterales isolates for comparison purposes.
Green = susceptible, yellow = intermediate, gray = resistant.

Table 4: Antibacterial activity of sulopenem against Enterobacterales urinary isolates non-susceptible to oral antimicrobial agents commonly used to treat UTI

Source	Resistant antibiotic(s) (MIC), N	Sulopenem $MIC_{50/90}$ (mg/L)	Sulopenem MIC ≤0.5 mg/L (S/I), n(%)	Sulopenem MIC ≥1 mg/L (R), n(%)
Community-acquired urinary isolates, N=507	Ciprofloxacin (MIC ≥1 mg/L), N=47	0.03/0.12	47 (100.0)	0 (0.0)
	TMP-SMX (MIC ≥4/76 mg/L), N=129	0.03/0.12	129 (100.0)	0 (0.0)
	Nitrofurantoin (MIC >64 mg/L), N=53	0.12/0.5	49 (92.5)	4 (7.5)
	ESBL phenotype (CTX MIC ≥4 mg/L), N=55	0.03/0.12	55 (100.0)	0 (0.0)
	Ciprofloxacin and ESBL phenotype, N=20	0.03/0.06	20 (100.0)	0 (0.0)
	Ciprofloxacin, TMP-SMX and ESBL phenotype, N=15	0.03/0.12	15 (100.0)	0 (0.0)
	Ciprofloxacin, TMP-SMX, nitrofurantoin and ESBL phenotype, N=6	--/--	6 (100.0)	0 (0.0)
	Multidrug resistant[a], N=21	0.06/0.5	21 (100.0)	0 (0.0)
All urinary isolates, N=728	Ciprofloxacin (MIC ≥1 mg/L), N=74	0.03/0.25	73 (98.6)	1 (1.4)
	TMP-SMX (MIC ≥4/76 mg/L), N=173	0.03/0.12	171 (98.8)	2 (1.2)
	Nitrofurantoin (MIC >64 mg/L), N=87	0.12/0.5	80 (92.0)	7 (8.0)
	ESBL phenotype (CTX MIC ≥4 mg/L), N=90	0.03/0.25	88 (97.8)	2 (2.2)
	Ciprofloxacin and ESBL phenotype, N=32	0.03/0.12	31 (96.9)	1 (3.1)
	Ciprofloxacin, TMP-SMX and ESBL phenotype, N=25	0.03/0.5	24 (96.0)	1 (4.0)
	Ciprofloxacin, TMP-SMX, nitrofurantoin and ESBL phenotype, N=7	--/--	7 (100.0)	0 (0.0)
	Multidrug resistant[a], N=35	0.03/0.5	34 (97.1)	1 (2.9)

Sulopenem $MIC_{50/90}$ data provided only when there are ≥10 isolates in a category. CTX = ceftriaxone; TMP-SMX = trimethoprim-sulfamethoxazole; S = susceptible; I = intermediate; R = resistant
[a]Multidrug resistant = isolate with ≥3 of the following: ESBL phenotype, ciprofloxacin resistant, TMP-SMX resistant, nitrofurantoin resistant

CONCLUSIONS

- Oral sulopenem etzadroxil/probenecid (ORLYNVAH™) was approved by the US FDA in October 2024 for the treatment of women with uncomplicated urinary tract infection (uUTI)
- Sulopenem demonstrated potent in vitro antimicrobial activity against contemporary Enterobacterales isolates, including:
  - ESBL-phenotype
  - Strains demonstrating co-resistance to commonly used oral antibacterial agents for treating uUTI
- These data support the recent approval of ORLYNVAH™ for adult female patients with uUTI who have limited or no alternative oral antibacterial treatment options