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Antimicrobial Activity of Gepotidacin against Clinical Isolates of *Escherichia coli* and *Staphylococcus saprophyticus* Collected Worldwide in 2019

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Introduction

- Gepotidacin (GSK2140944) is a novel triazaacenaphthylene bacterial type II topoisomerase inhibitor in Phase 3 clinical development for the treatment of uncomplicated urinary tract infections (UTI) and gonorrhea
- Gepotidacin inhibits bacterial DNA gyrase and topoisomerase IV by a unique mechanism
- This study reports on interim results from a global surveillance program to monitor the *in vitro* activity of gepotidacin and comparator agents when tested against contemporary *Escherichia coli* and *Staphylococcus saprophyticus* clinical isolates collected from patients with UTIs worldwide as part of the SENTRY Antimicrobial Surveillance Program

Materials and Methods

- A total of 1,467 *E. coli* and 92 *S. saprophyticus* isolates were collected from 73 medical centers located in the US (38 centers), Europe (27 centers in 14 countries), Asia-Pacific region (4 centers in Japan), and Latin America (4 centers in 3 countries)
- Isolates were from urinary tract infections, 70% of which were isolated from ambulatory, emergency, family practice, and outpatient medical services commonly associated with community acquired UTI
- Isolates were tested for susceptibility by CLSI reference methods in a central laboratory (JMI Laboratories)
- Susceptibility to mecillinam and fosfomycin was determined by agar dilution, and the latter included glucose-6-phosphate (25 µg/mL)
- MICs for comparators were interpreted, where available, according to CLSI and EUCAST criteria
- The extended-spectrum β-lactamase (ESBL) phenotype in *E. coli* was characterized by isolates displaying ceftriaxone MIC values ≥2µg/mL

Results

- Gepotidacin ($MIC_{50/90}$, 2/4 µg/mL) displayed activity against 1,467 *E. coli* isolates (Tables 1 and 4)
- Susceptibility rates of trimethoprim-sulfamethoxazole ($MIC_{50/90}$, ≤0.12/>16 µg/mL), ciprofloxacin ($MIC_{50/90}$, 0.015/>4 µg/mL), and amoxicillin-clavulanate ($MIC_{50/90}$, 8/16 µg/mL) were 67.1%, 72.9%, and 78.6% (CLSI), respectively (Table 1)
- Susceptibility rates of 99.0% for fosfomycin ($MIC_{50/90}$, 0.5/1 µg/mL), 97.4% for nitrofurantoin ($MIC_{50/90}$, 16/32 µg/mL), and 100% for meropenem (≤0.015/0.03 µg/mL) were seen against *E. coli* isolates (Table 1)
- Gepotidacin ($MIC_{50/90}$, 0.06/0.12 µg/mL) also was active against 92 *S. saprophyticus* isolates, with 100% of isolates inhibited at ≤0.25 µg/mL (Table 2)
- Susceptibility of *S. saprophyticus* isolates to trimethoprim-sulfamethoxazole, ciprofloxacin, or nitrofurantoin was 98.9-100% (CLSI), while fosfomycin showed little activity ($MIC_{50/90}$, 64/>256 µg/mL; 1.1% susceptible [EUCAST]) (Table 2)
- An ESBL phenotype was observed in 15.2% of *E. coli* isolates, and gepotidacin ($MIC_{50/90}$, 2/4 µg/mL) remained active against these isolates with activity similar to that obtained against non-ESBL *E. coli* ($MIC_{50/90}$, 2/2 µg/mL; Table 3)
- Activities of ciprofloxacin ($MIC_{50/90}$, >4/>4 µg/mL; 16.6% susceptible), cefazolin ($MIC_{50/90}$, >32/>32 µg/mL; 0.0% susceptible) and trimethoprim/sulfamethoxazole ($MIC_{50/90}$ >16/>16 µg/mL; 39.0% susceptible) were limited against ESBL isolates (Table 3)
- The oral drugs fosfomycin ($MIC_{50/90}$, 0.5/1 µg/mL; 96.9% susceptible) and nitrofurantoin ($MIC_{50/90}$, 16/32 µg/mL; 92.4% susceptible) remained active against ESBL isolates (Table 3)
- Similar MIC distributions and activities for gepotidacin were observed for isolates collected from outpatient and inpatient settings with 98.2% of all observed MIC results at ≤4 µg/mL (Table 4)

Gepotidacin demonstrated potent *in vitro* activity against contemporary *E. coli* and *S. saprophyticus* isolates causing UTI worldwide.

Gepotidacin retained *in vitro* activity against phenotypic ESBL *E. coli* where some oral and intravenous options were limited.

Table 1 Activity of gepotidacin and comparator antimicrobial agents tested against 1,467 *Escherichia coli* isolates

Antimicrobial agent	No. of isolates[a]	µg/L			CLSI[b]			EUCAST[b]		
		MIC_{50}	MIC_{90}	MIC range	%S	%I	%R	%S	%I	%R
Gepotidacin	1,467	2	4	0.06 to 32	—	—	—	—	—	—
Ciprofloxacin	1,466	0.015	>4	≤0.002 to >4	72.9	1.8	25.2	72.9	1.8	25.2
Levofloxacin	1,458	0.03	16	≤0.015 to >32	74.1	0.9	25.0	74.1	0.9	25.0
Fosfomycin	1,467	0.5	1	≤0.12 to >256	99.0 [c]	0.3	0.6	96.9 [d]		3.1
Mecillinam	1,467	0.5	8	0.06 to >32	92.9 [c]	1.6	5.5	92.9 [d]		7.1
Nitrofurantoin[i]	1,466	16	32	≤2 to >128	97.4	1.4	1.2	98.8 [d]		1.2
Trimethoprim-Sulfamethoxazole[i]	1,464	≤0.12	>16	≤0.12 to >16	67.1		32.9	67.1	0.8	32.1
Trimethoprim	1,466	0.5	>8	0.03 to >8	66.2		33.8	66.0 [d]		34.0
Sulfisoxazole	1,466	128	>256	≤4 to >256	59.6		40.4	—	—	—
Ampicillin	1,466	>64	>64	≤1 to >64	45.6	0.5	53.9	45.6 [d]		54.4
Amoxicillin-clavulanate										
IV	1,316	8	16	0.5 to >32	78.6	15.5	5.9	78.6		21.4
ORAL					78.6	15.5	5.9	98.4 [d]		1.6
Piperacillin-Tazobactam	1,461	2	4	0.25 to >128	97.5	1.2	1.3	94.9	2.7	2.5
Ceftazidime-Avibactam	1,465	0.12	0.25	≤0.015 to 1	100.0		0.0	100.0		0.0
Ceftolozane-Tazobactam	1,465	0.25	0.5	≤0.12 to >16	99.5	0.3	0.2	99.5		0.5
Cefazolin										
IV	1,314	2	>32	≤0.5 to >32	58.8 [e]	12.9	28.3		71.7 [f,g]	28.3
uUTI					80.1 [h]		19.9		71.7 [f,g]	28.3
Ceftriaxone	1,465	≤0.06	>8	≤0.06 to >8	84.6	0.1	15.2	84.6	0.1	15.2
Meropenem	1,465	≤0.015	0.03	≤0.015 to 1	100.0	0.0	0.0	100.0	0.0	0.0
Amikacin	1,465	2	8	≤0.25 to >32	99.7	0.1	0.3	98.5 [i]		1.5
Gentamicin	1,465	0.5	4	≤0.12 to >16	90.3	0.2	9.5	89.8 [i]		10.2

[a] Not all isolates were tested against all drugs at time of publication and represents interim data
[b] Criteria as published by CLSI (2020) and EUCAST (2020).
[c] Using oral breakpoints for urinary tract infection caused by *E. coli*.
[d] Using oral breakpoints for uncomplicated urinary tract infection.
[e] Using parenteral breakpoints for infection other than uncomplicated urinary tract.
[f] Intermediate can be interpreted as susceptible if drug exposure can be increased with a higher dosing regimen or higher concentration at the infection site (EUCAST 2020).
[g] Using parenteral breakpoints for urinary tract infection caused by *E. coli*.
[h] Using parenteral breakpoints for urinary tract infection.
[i] For infections originating from the urinary tract.
[j] Used only or for primarily treating UTIs.

Table 2 Activity of gepotidacin and comparator antimicrobial agents tested against 92 *Staphylococcus saprophyticus* isolates

Antimicrobial agent	No. of isolates	µg/mL			CLSI[a]			EUCAST[a]		
		MIC_{50}	MIC_{90}	MIC range	%S	%I	%R	%S	%I	%R
Gepotidacin	92	0.06	0.12	≤0.03 to 0.25						
Ciprofloxacin	92	0.25	0.5	0.25 to 0.5	100.0	0.0	0.0	[b]	100.0	0.0
Levofloxacin	92	0.5	0.5	0.25 to 1	100.0	0.0	0.0	[b]	100.0	0.0
Nitrofurantoin	92	16	32	8 to 32	100.0	0.0	0.0	100.0 [c]		0.0
Vancomycin	92	1	2	0.5 to 2	100.0	0.0	0.0	100.0		0.0
Trimethoprim-Sulfamethoxazole	92	≤0.5	≤0.5	≤0.5 to >16	98.9		1.1	98.9	0.0	1.1
Trimethoprim	92	0.25	0.5	0.12 to >8				95.7 [c]		4.3
Sulfisoxazole	92	32	256	8 to >256						
Penicillin	92	0.25	0.5	0.12 to >2	1.1		98.9			
Fosfomycin	92	64	>256	32 to >256				1.1 [d]		98.9

[a] Criteria as published by CLSI (2020) and EUCAST (2020).
[b] An arbitrary susceptible breakpoint of ≤0.001 µg/mL has been published by EUCAST indicating that susceptible should not be reported for this organism-agent combination and intermediate should be interpreted as "susceptible increased exposure" (EUCAST 2020).
[c] Using uncomplicated urinary tract infection only breakpoints.
[d] Administered via IV formulation

Table 3. Distribution of MIC values for gepotidacin and comparator antimicrobial agents tested against ESBL and non-ESBL *Escherichia coli*

Antimicrobial Agent	No. of Isolates[a]	MIC (µg/mL) ≤0.12	0.25	0.5	1	2	4	8	16	32	64	128	256
Non-ESBL E. coli isolates													
Gepotidacin	1,242	3 0.2%	10 1.0%	41 4.3%	374 34.5%	696 90.5%	106 99.0%	10 99.8%	2 100.0%				
Ciprofloxacin	1,242	973 78.3%	58 83.0%	19 84.5%	7 85.1%	3 85.3%	5 85.7%	177[b] 100.0%					
Trimethoprim/ sulfamethoxazole	1,241	783 63.1%	58 67.8%	42 71.2%	7 71.7%	6 72.2%	9 72.9%	6 73.4%	2 73.6%	328[b] 100.0%			
Amoxicillin/ clavulanic acid	1,116		0 0.0%	3 0.3%	20 2.1%	143 14.9%	438 54.1%	327 83.4%	140 96.0%	35 99.1%	10[b] 100.0%		
Meropenem	1,242	1241 99.9%	99.9%	1 100.0%									
Cefazolin	1,114			2 0.2%	342 30.9%	428 69.3%	170 84.6%	69 90.8%	42 94.5%	32 97.4%	29[b] 100.0%		
Ceftriaxone	1,242	1203 96.9%	26 99.0%	6 99.4%	5 99.8%	2 100.0%							
Fosfomycin	1,241	2 0.2%	66 5.5%	783 68.6%	312 93.7%	48 97.6%	7 98.1%	6 98.6%	1 98.7%	3 99.0%	6 99.4%	4 99.8%	3[b] 100.0%
Nitrofurantoin	1,241					14 1.1%	35 3.9%	300 28.1%	700 84.5%	171 98.3%	11 99.2%	7 99.8%	3[b] 100.0%
Amikacin	1,242		2 0.2%	1 0.2%	55 4.7%	651 57.1%	444 92.8%	86 99.8%	3 100.0%				
ESBL E. coli isolates													
Gepotidacin	223	0 0	0 0.0%	12 5.4%	69 36.3%	100 81.2%	28 93.7%	6 96.4%	5 98.7%	3 100.0%			
Ciprofloxacin	223	31 13.9%	6 16.6%	8 20.2%	2 21.1%	2 22.0%	4 23.8%	170[b] 100.0%					
Trimethoprim/ sulfamethoxazole	223	75 33.6%	8 37.2%	2 38.1%	1 38.6%	1 39.0%	2 39.9%	2 40.8%	40.8%	132[b] 100.0%			
Amoxicillin/ clavulanic acid	200				0 0.0%	2 1.0%	35 18.5%	68 52.5%	63 84.0%	21 94.5%	11[b] 100.0%		
Meropenem	223	222 99.6%	0 99.6%	0 99.6%	1 100.0%								
Cefazolin	200									0 0.0%	200[b] 100.0%		
Ceftriaxone	223					0 0.0%	6 2.7%	4 4.5%	213[b] 100.0%				
Fosfomycin	223	0 0.0%	6 2.7%	143 66.8%	52 90.1%	8 93.7%	1 94.2%	2 95.1%	95.1%	1 95.5%	3 96.9%	1 97.3%	6[b] 100.0%
Nitrofurantoin	223					1 0.4%	2 1.3%	65 30.5%	111 80.3%	27 92.4%	9 96.4%	7 99.6%	1[b] 100.0%
Amikacin	223		0 0.0%	1 0.4%	9 4.5%	83 41.7%	68 72.2%	43 91.5%	14 97.8%	1 98.2%	4[b] 100.0%		

Shading indicates breakpoints according to CLSI (2020) with susceptible highlighted in green, intermediate in yellow, resistant in red. Concentrations not tested are represented in gray.
[a] Not all isolates were tested against all drugs at time of publication and represents interim data
[b] Represent MIC values greater than the highest concentration tested

Table 4 Distribution of MIC values for gepotidacin tested against *Escherichia coli* isolates from ambulatory, emergency, family practice, and outpatient or other medical services

Antimicrobial Agent	No. of isolates[a]	MIC (µg/mL) ≤0.25	0.5	1	2	4	8	16	32	MIC_{50}	MIC_{90}
Ambulatory, emergency, family practice, and outpatient											
Gepotidacin	1,008[a]	6 0.6%	37 4.3%	304 34.4%	550 89.0%	93 98.2%	11 99.3%	5 99.8%	2 100.0%	2	4
Other[b]											
Gepotidacin	459[a]	7 1.5%	16 5.0%	140 35.5%	247 89.3%	41 98.3%	5 99.3%	2 99.8%	1 100.0%	2	4

[a] EBSL rates observed for ambulatory, emergency, family practice, and outpatient isolates were 12.8% compared to 20.5% for other isolates.
[b] Other medical services include: cardiothoracic/pulmonary, dialysis, general/GI, geriatrics, hematology/oncology, infectious disease, intensive care unit, internal medicine, long term care, neurology, neurosurgery, obstetrics/gynecology, orthopedics, pediatrics/neonate, rehabilitation, renal, surgery, transplant, trauma, urology/prostate

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