In vitro activity of gepotidacin and comparator agents against a collection of *Escherichia coli* and *Klebsiella pneumoniae* urine isolates from the United States during 2023

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Gepotidacin demonstrated *in vitro* activity against contemporary *E. coli* and *K. pneumoniae*, including ESBL-producing and MDR isolates.

Digital poster

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Introduction

- Gepotidacin, a novel, bactericidal, first-in-class triazaacenaphthylene antibacterial, inhibits bacterial DNA replication by a distinct binding site, unique mechanism of action and for most pathogens, well-balanced inhibition of two type II topoisomerases[1-3].
- Gepotidacin was recently approved for the treatment of uncomplicated urinary tract infections (uUTI) caused by the following susceptible microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, Citrobacter freundii complex, *Staphylococcus saprophyticus*, and Enterococcus faecalis.
- This study reports a subset of data from a global surveillance study testing *in vitro* activity of gepotidacin and other oral antibiotics against contemporary *E. coli* and *K. pneumoniae* isolates collected from patients with UTI in the United States.

Table 1 Activity of gepotidacin and other oral agents tested against *E. coli* and *K. pneumoniae* UTI isolates collected from medical centers in the United States during 2023

Organism (No. Isolates)	µg/mL			Percent Susceptibilities [a]		
Antimicrobial Agent	MIC_{50}	MIC_{90}	MIC Range	%S	%I	%R
E. coli (1,011)						
Gepotidacin [b]	2	4	0.12 to 16	100.0		
Ciprofloxacin	0.015	>4	≤0.002 to >4	80.3	2.2	17.5
Levofloxacin	0.03	8	≤0.015 to >32	82.3	0.7	17.0
Amoxicillin-clavulanic acid	4	16	0.5 to >32	88.1	7.8	4.1
Ampicillin	8	>64	≤1 to >64	51.8	0.5	47.7
Nitrofurantoin [c]	16	32	≤2 to >128	97.4	0.7	1.9
Trimethoprim-sulfamethoxazole	≤0.12	>4	≤0.12 to >4	71.5		28.5
Fosfomycin [c, d]	0.5	1	≤0.12 to >256	99.2	0.4	0.4
Mecillinam [c,d]	0.25	4	0.03 to 32	94.9	1.8	3.4
K. pneumoniae (398)						
Gepotidacin [b]	4	16	1 to >64	92.5	5.3	2.3
Ciprofloxacin	0.015	1	0.004 to >4	82.4	6.5	11.1
Levofloxacin	0.06	1	≤0.015 to >32	88.7	4.0	7.3
Amoxicillin-clavulanic acid	2	8	0.5 to >32	90.4	5.3	4.3
Ampicillin	64	>64	≤1 to >64	3.3	9.6	87.2
Nitrofurantoin [c]	64	>128	≤2 to >128	28.4	30.4	41.2
Trimethoprim-sulfamethoxazole	≤0.12	>4	≤0.12 to >4	81.4		18.6
Fosfomycin [d, e]	8	32	0.5 to >256	-	-	-

[a] Interpreted by CLSI breakpoints, unless otherwise specified.
[b] Using FDA susceptible breakpoints.
[c] Using uncomplicated urinary tract infection only breakpoints.
[d] Tested by agar dilution.
[e] Breakpoints not established.

Results

K. pneumoniae

- Gepotidacin displayed activity ($MIC_{50/90}$ of 4/16 µg/mL) against all 398 *K. pneumoniae* isolates (Table 1).
- 92.5% of all observed gepotidacin MICs were ≤16 µg/mL (FDA susceptible breakpoint, Table 2).
- Susceptibility rates for *K. pneumoniae* isolates against all oral comparators tested were below 91% (Table 1).
  - Ciprofloxacin (82.4%)
  - Levofloxacin (88.7%)
  - Amoxicillin-clavulanic acid (90.4%)
  - Ampicillin (3.3%)
  - Nitrofurantoin (28.4%)
  - Trimethoprim-sulfamethoxazole (81.4%)
- Gepotidacin MIC_{50} and MIC_{90} values ranged from 4 – 16 ug/mL and 16 – 64 ug/mL, respectively, against drug-NS subsets of *K. pneumoniae*.
- 64.3-90.5% of the drug-NS isolates of *K. pneumoniae* were susceptible to gepotidacin.
- 16.8% and 14.1% of *K. pneumoniae* isolates displayed ESBL and MDR phenotypes, respectively.
- Gepotidacin $MIC_{50/90}$ values against ESBL and MDR isolates were 16/32 mg/L and 16/64 mg/L, with 72% and 68% isolates respectively, inhibited at <=16 ug/mL (FDA susceptible breakpoint).

E. coli

- Gepotidacin displayed activity ($MIC_{50/90}$ of 2/4 µg/mL) against all 1,011 *E. coli* isolates (Table 1).
- 100.0% of all observed gepotidacin MICs were ≤16 µg/mL (FDA susceptible breakpoint, Table 2).
- Susceptibility rates for *E. coli* isolates against most comparators tested were below 90% (Table 1).
  - Ciprofloxacin (80.3%)
  - Levofloxacin (82.3%)
  - Amoxicillin-clavulanic acid (88.1%)
  - Ampicillin (51.8%)
  - Trimethoprim-sulfamethoxazole (71.5%)
- Susceptibility rates for *E. coli* isolates against some comparators tested were above 94% (Table 1).
  - Nitrofurantoin (97.4%)
  - Fosfomycin (99.2%)
  - Mecillinam (94.9%)
- Gepotidacin MIC_{50} ranged from 1 – 2 ug/mL and MIC_{90} values were 4 µg/mL against drug-NS subsets of *E. coli* (Table 2)
- 100% of the drug-NS isolates of *E. coli* were susceptible to gepotidacin.
- 14.5% and 12.1% of *E. coli* isolates displayed ESBL and MDR phenotypes, respectively.
- Gepotidacin remained active against *E. coli* ESBL and MDR isolates with $MIC_{50/90}$ values of 2/4 µg/mL for both subsets (Table 2).

Methods

- 1,011 *E. coli* and 398 *K. pneumoniae* isolates were collected during 2023 from 58 medical centers located in the United States.
- All Isolates were cultured from urine specimens collected from patients seen mostly (65%) in ambulatory, emergency, family practice, and outpatient services.
- Bacterial identifications were confirmed by MALDI-TOF MS.
- All isolates were tested for susceptibility by CLSI methods[4] at a central laboratory (Element Iowa City).
- Susceptibility to fosfomycin and mecillinam were determined by agar dilution.
- MIC results for gepotidacin and comparator agents were interpreted per FDA[5] and CLSI guidelines[6] to determine % of susceptible (S), intermediate (I), and resistant (R) isolates.
- MIC results for oral antibiotics licensed for the treatment of uUTI, were interpreted per CLSI criteria to identify not susceptible (NS), multidrug-resistant (MDR) and extended-spectrum β-lactamase (ESBL)-positive subsets.
- The ESBL phenotype was characterized as isolates displaying aztreonam, ceftazidime, or ceftriaxone MIC values ≥ 2 µg/mL.
- The MDR phenotype was defined as described by Magiorakos et al.[7] as having a CLSI-not susceptible phenotype to 3 or more drug classes from the following: extended-spectrum cephalosporins (ceftriaxone or ceftazidime); carbapenems (meropenem); antipseudomonal penicillins + β-lactamase inhibitors (piperacillin-tazobactam); fluoroquinolones (ciprofloxacin or levofloxacin); and aminoglycosides (gentamicin or amikacin).

Table 2 Frequency distribution of gepotidacin MIC values for *E. coli* and *K. pneumoniae* isolate subsets from the United States in 2023 with not susceptible to oral agents

Organism (No. isolates)	No. and cumulative % of isolates inhibited at a gepotidacin MIC (µg/mL) of:									Gepotidacin		
Phenotypic subset [a]	≤0.25	0.5	1	2	4	8	16	32	64	>64	MIC_{50}	MIC_{90}	%S
E. coli (1,011)	16 1.6%	77 9.2%	373 46.1%	438 89.4%	82 97.5%	17 99.2%	8 100%				2	4	100%
ESBL positive (147)	3 2.0%	17 13.6%	42 42.2%	57 81.0%	17 92.5%	9 98.6%	2 100%				2	4	100%
MDR (122)	2 1.6%	13 12.3%	35 41.0%	46 78.7%	20 95.1%	5 99.2%	1 100%				2	4	100%
Fluoroquinolone-NS (199)	8 4.0%	26 17.1%	63 48.7%	61 79.4%	22 90.5%	12 96.5%	7 100%				2	4	100%
Amoxicillin-clavulanic acid-NS (120)	3 2.5%	6 7.5%	40 40.8%	53 85.0%	13 95.8%	3 98.3%	2 100%				2	4	100%
Ampicillin-NS (487)	9 1.8%	51 12.3%	168 46.8%	195 86.9%	41 95.3%	15 98.4%	8 100%				2	4	100%
Nitrofurantoin-NS [b] (26)	1 3.8%	4 19.2%	4 34.6%	12 80.8%	4 96.2%	0 96.2%	1 100%				2	4	100%
Trimethoprim-sulfamethoxazole-NS (288)	3 1.0%	34 12.8%	100 47.6%	112 86.5%	29 96.5%	7 99.0%	3 100%				2	4	100%
Fosfomycin-NS [b,c] (8)		0 0%	3 37.5%	2 62.5%	2 87.5%	1 100%					2	ND	100%
Mecillinam-NS [b,c] (52)	2 3.8%	5 13.5%	19 50.0%	20 88.5%	6 100%						1	4	100%
K. pneumoniae (398)		0 0%	1 0.3%	10 2.8%	190 50.5%	129 82.9%	38 92.5%	21 97.7%	5 99%	4 100%	4	16	92.5%
ESBL positive (67)				0 0%	12 17.9%	21 49.3%	15 71.6%	13 91.0%	2 94.0%	4 100%	16	32	71.6%
MDR (56)				0 0%	8 14.3%	18 46.4%	12 67.9%	12 89.3%	2 92.9%	4 100%	16	64	67.9%
Fluoroquinolone-NS (70)				0 0%	9 12.9%	18 38.6%	18 64.3%	16 87.1%	5 94.3%	4 100%	16	64	64.3%
Amoxicillin-clavulanic acid-NS (38)				0 0%	7 18.4%	15 57.9%	7 76.3%	6 92.1%	1 94.7%	2 100%	8	32	76.3%
Nitrofurantoin-NS [b] (285)			0 0%	6 2.1%	141 51.6%	81 80.0%	30 90.5%	18 96.8%	5 98.6%	4 100%	4	16	90.5%
Trimethoprim-sulfamethoxazole-NS (74)				0 0%	14 18.9%	19 44.6%	18 68.9%	15 89.2%	4 94.6%	4 100%	16	64	68.9%

ND, not determined due to small number of isolates; NS, not susceptible.
[a] Interpreted by CLSI breakpoints.
[b] Using uncomplicated urinary tract infection only breakpoints.
[c] Tested by agar dilution.

Conclusions

- Gepotidacin demonstrated *in vitro* activity against contemporary *E. coli* and *K. pneumoniae* UTI isolates from the United States.
  - 100.0% of *E. coli* and 92.5% of *K. pneumoniae* isolates were inhibited by gepotidacin at or below the FDA approved susceptible breakpoint of ≤16 µg/mL.
- Among the comparator agents tested, only nitrofurantoin, fosfomycin, and mecillinam had susceptibility rates greater than 90% against *E. coli* isolates while no agents had susceptibility rates greater than 91% against *K. pneumoniae* UTI isolates from the United States.
- Against *E. coli*, gepotidacin activity remained mostly unaffected by resistance to other oral standard-of-care antibiotics and 100% of the drug-NS isolates of *E. coli* remained susceptible to gepotidacin, while 64.3-90.5% of drug-NS *K. pneumoniae* isolates were susceptible to gepotidacin.

Abbreviations

CLSI, Clinical and Laboratory Standards Institute; ESBL, extended-spectrum β-lactamase; I, intermediate; MDR, multidrug resistance; MIC, Minimal inhibitory concentration; NS, not susceptible; ND, not determined; S, susceptible; R, resistant; UTI, urinary tract infection

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Acknowledgments

This study has been funded in whole or in part with federal funds from the U.S. Department of Health and Human Services; Administration for Strategic Preparedness and Response; Biomedical Advanced Research and Development Authority under contract HHSO100201300011C.

Disclosures

This study at Element Iowa City was supported by GSK. Element Iowa City received compensation fees for services in relation to preparing the poster. SJRA and REM are employees of Element Iowa City (JMI Laboratories). RK and NSO are employees of the GSK group of companies.

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