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In Vitro Activity of Gepotidacin and Eight Comparator Agents against 4,000 Recent Clinical Isolates

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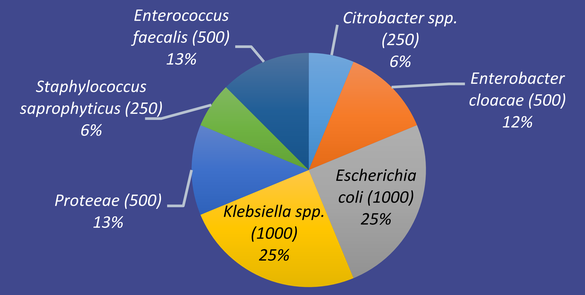
Introduction

- Gepotidacin (GSK2140944) is a novel, bactericidal, first in class triazaacenaphthylene antibiotic in clinical development for the treatment of gonorrhea and uncomplicated urinary tract infection (acute cystitis).
- Gepotidacin selectively inhibits bacterial DNA replication by a distinct mechanism of action, which confers *in vitro* activity against most strains of target pathogens, such as *Escherichia coli, Staphylococcus saprophyticus* and *Neisseria gonorrhoeae,* including those resistant to current antibiotics.
- In this study, minimum inhibitory concentrations (MICs) were determined by broth microdilution for gepotidacin and eight comparator agents against 4,000 recent gram-negative and gram-positive clinical isolates associated with uncomplicated urinary tract infections.

Methods

- A total of 3,250 gram-negative and 750 gram-positive isolates collected in global surveillance studies from 2012-2020 (primarily 2019-2020 with 60% from the United States, 20% from Europe and 20% from the rest of world for each species) were included in this study. The species tested are shown in Figure 1.
- A total of 3980 (99.5%) isolates were from urinary sources.
- MIC endpoints for gepotidacin and 8 comparators were determined by broth microdilution following CLSI guidelines [4] for all compounds except fosfomycin. Fosfomycin MIC endpoints were determined by agar dilution following CLSI guidelines [4, 5].
- The minimum bactericidal concentration (MBC) of gepotidacin was determined for 50 isolates chosen at random (5 from each species or genus group) [6].

Figure 1. Distribution of species tested



Citrobacter spp. (n): *C. amalonaticus* (7); *C. braakii* (7); *C. farmeri* (2); *C. freundii* (126); *C. koseri* (106); *C. murliniae* (1); *C. youngae* (1)
Klebsiella spp. (n): *K. aerogenes* (250); *K. oxytoca* (250); *K. pneumoniae* (500)
Proteeae (n): *Proteus mirabilis* (250); *Providencia rettgeri* (250)

Figure 2. MIC distribution of gepotidacin by species

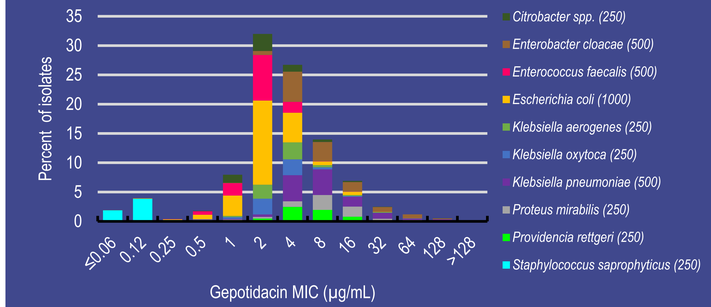


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Table 1. Activity of gepotidacin against species commonly associated with urinary tract infections, including resistant subsets

Organism (N total/CIP NS/ESBL+)	$MIC_{50/90}$ (µg/mL)		
	All	CIP NS	ESBL+*
All Gram-negative (3250/850/422*)	4/16	4/32	4/16
Escherichia coli (1000/352/228)	2/4	2/4	2/8
Citrobacter spp. (250/24/na)	2/8	4/16	na
Enterobacter cloacae (500/126/na)	8/32	16/64	na
Klebsiella pneumoniae (500/162/145)	4/32	16/64	16/32
Klebsiella aerogenes (250/22/na)	4/8	8/32	na
Klebsiella oxytoca (250/32/28)	4/4	2/16	4/16
Proteus mirabilis (250/84/21)	8/16	4/32	16/64
Providencia rettgeri (250/48/na)	16/16	8/128	na
Enterococcus faecalis (500/149/na)	2/4	1/4	na
Staphylococcus saprophyticus (250 /0/na)	0.12/0.12	na	na

CIP NS, ciprofloxacin not susceptible based on CLSI 2022 guidelines [5]; na, not applicable
* ESBL+, ceftazidime ≥2 µg/mL for *E. coli*, *K. pneumoniae*, *K. oxytoca* & *P. mirabilis* only

Table 2. *In vitro* activity of gepotidacin and comparators

Organism	Compound	MIC_{90}	MIC Range	%S
E. coli (n=1,000)	Gepotidacin	4	0.12 - 64	na
	Ceftazidime	>16	≤0.03 - >16	81.8
	Ciprofloxacin	64	0.004 - >128	64.8
	Doxycycline	>16	0.25 - >16	65.1
	Fosfomycin	16	0.5 - >256	98.0
	Meropenem	0.03	≤0.004 - >8	99.5
	Nitrofurantoin	16	≤0.5 - >128	96.3
	Piperacillin/tazobactam	8	≤0.12 - >128	95.7
	Trimethoprim/sulfamethoxazole	>4	≤0.06 - >4	63.4
E. coli CIP NS (n=352)	Gepotidacin	4	0.25 - 64	na
	Ceftazidime	> 16	≤0.03 - > 16	58.8
	Ciprofloxacin	128	0.5 - > 128	0.0
	Doxycycline	> 16	0.5 - > 16	44.0
	Fosfomycin*	16	0.5 - > 256	97.4
	Meropenem	0.06	0.015 - > 8	98.9
	Nitrofurantoin	32	≤0.5 - > 128	93.8
	Piperacillin/tazobactam	16	≤0.12 - > 128	90.3
	Trimethoprim/sulfamethoxazole	> 4	≤0.06 - > 4	42.1
E. coli ESBL+ (n=228)	Gepotidacin	8	0.25 - 16	na
	Ceftazidime	> 16	2 - > 16	20.2
	Ciprofloxacin	128	0.008 - > 128	25.0
	Doxycycline	> 16	0.25 - > 16	41.2
	Fosfomycin*	16	0.5 - > 256	96.5
	Meropenem	0.06	0.015 - > 8	97.8
	Nitrofurantoin	32	≤0.5 - 128	93.0
	Piperacillin/tazobactam	32	≤0.12 - > 128	87.7
	Trimethoprim/sulfamethoxazole	> 4	≤0.06 - > 4	40.4
K. pneumoniae (n=500)	Gepotidacin	32	0.5 - >128	na
	Ceftazidime	>16	≤0.03 - >16	73.6
	Ciprofloxacin	64	0.008 - >128	67.6
	Doxycycline	>16	1 - >16	68.2
	Fosfomycin*	>256	1 - >256	na
	Meropenem	0.12	0.015 - >8	92.4
	Nitrofurantoin	>128	2 - >128	23.2
	Piperacillin/tazobactam	>128	0.5 - >128	81
	Trimethoprim/sulfamethoxazole	>4	≤0.06 - >4	69.4
K. pneumoniae CIP NS (n=162)	Gepotidacin	64	0.5 - > 128	na
	Ceftazidime	> 16	0.06 - > 16	25.9
	Ciprofloxacin	> 128	0.5 - > 128	0
	Doxycycline	> 16	1 - > 16	28.4
	Fosfomycin*	> 256	8 - > 256	na
	Meropenem	> 8	0.015 - > 8	79.0
	Nitrofurantoin	> 128	16 - > 128	10.5
	Piperacillin/tazobactam	> 128	1 - > 128	52.5
	Trimethoprim/sulfamethoxazole	> 4	≤0.06 - > 4	22.8
K. pneumoniae ESBL+ (n=145)	Gepotidacin	32	1 - >128	na
	Ceftazidime	>16	2 - >16	9.0
	Ciprofloxacin	>128	0.008 - >128	13.8
	Doxycycline	>16	1 - >16	29.7
	Fosfomycin*	>256	8 - >256	na
	Meropenem	>8	0.015 - >8	73.8
	Nitrofurantoin	>128	2 - >128	10.4
	Piperacillin/tazobactam	>128	1 - >128	41.4
	Trimethoprim/sulfamethoxazole	>4	≤0.06 - >4	22.1

MIC_{90} and MIC range in µg/mL; %S, percent susceptible [5]; CIP NS, ciprofloxacin not susceptible; ESBL+, ceftazidime MIC ≥2 µg/mL; na, not applicable

Results

- Gepotidacin was active against the gram-negative isolates tested with $MIC_{50/90}$ values of 4/16 µg/mL. MIC_{90} values ranged from 32 µg/mL for *Enterobacter cloacae* and *Klebsiella pneumoniae*, 16 µg/mL for *Proteus mirabilis* and *Providencia rettgeri*, 8 µg/mL for *Citrobacter* spp. and *Klebsiella aerogenes*, to 4 µg/mL for *Escherichia coli* and *Klebsiella oxytoca* (Table 1, Figure 2).
- Gepotidacin showed potent *in vitro* activity against *Enterococcus faecalis* and *Staphylococcus saprophyticus* with $MIC_{50/90}$ values of 2/4 µg/mL and 0.12/0.12 µg/mL, respectively (Table 1, Figure 2).
- Gepotidacin maintained activity against ciprofloxacin not susceptible gram-negative isolates ($MIC_{50/90}$ = 4/32 µg/mL), ESBL+ gram-negative isolates ($MIC_{50/90}$ = 4/16 µg/mL), and ciprofloxacin not susceptible *E. faecalis* ($MIC_{50/90}$ = 1/4 µg/mL) (Table 1).
- Gepotidacin activity against all *E. coli* was MIC_{90}=4 µg/mL; MIC_{90}=4 µg/mL against ciprofloxacin not susceptible isolates, and MIC_{90}=8 µg/mL against ESBL+ isolates. (Tables 1 & 2).
- Gepotidacin was bactericidal against most isolates tested, with 94% (47/50) exhibiting an MBC/MIC ratio of ≤4 (data not shown).

Conclusion

Gepotidacin demonstrated *in vitro* activity against 4,000 recent gram-negative and gram-positive clinical isolates, including ESBL+ isolates and those not susceptible to ciprofloxacin.

References

1. Overcash JS, Tiffany CA, Scangarella-Oman NE, Perry CR, Tao Y, Hossain M, Barth A, Dumont EF. 2020. *Phase 2a pharmacokinetic, safety, and exploratory efficacy evaluation of oral gepotidacin (GSK2140944) in female participants with uncomplicated urinary tract infection (acute uncomplicated cystitis*). Antimicrob Agents Chemother 64:e00199-20.
2. Taylor SN, Morris DH, Avery AK, Workowski KA, Batteiger BE, Tiffany CA, Perry CR, Raychaudhuri A, Scangarella-Oman NE, Hossain M, Dumont EF. 2018. *Gepotidacin for the treatment of uncomplicated urogenital gonorrhea: a Phase 2, randomized, dose-ranging, single-oral dose evaluation*. Clin Infect Dis 67:504-512
3. Gibson EG, Bax B, Chan PF, Osheroff N. *Mechanistic and Structural Basis for the Actions of the Antibacterial Gepotidacin against Staphylococcus aureus Gyrase*. ACS Infect Dis. 2019 Apr 12;5(4):570-581. doi: 10.1021/acsinfecdis.8b00315. Epub 2019 Feb 28. PMID: 30757898; PMCID: PMC6461504.
4. Clinical Laboratory Standards Institute (CLSI), 2018. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standards – Eleventh Edition*. CLSI document M07-A11 (ISBN 1-56238-836-3). CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
5. Clinical and Laboratory Standards Institute (CLSI), 2022. *Performance Standards for Antimicrobial Susceptibility Testing*. 32nd Ed. CLSI Supplement M100 (ISBN 978-1-68440-134-5). CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
6. NCCLS (now Clinical and Laboratory Standards Institute). *Methods for Determining Bactericidal Activity of Antimicrobial Agents; Approved Guideline*. NCCLS document M26-A [ISBN 1-56238-384-1]. NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087 USA, 1999.)

Disclosures

JW and NSO are employees of, and hold shares in, GlaxoSmithKline plc. MH and DS report no conflicts of interest. This study was performed at IHMA and funded by GlaxoSmithKline.