In Vitro Activity of Gepotidacin and Comparators Against a Collection of *E. coli* and *S. saprophyticus* Urine Isolates Collected from Europe during 2019–2020

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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 gonorrhea and uncomplicated urinary tract infections (UTIs).
- Gepotidacin inhibits bacterial DNA gyrase and topoisomerase IV by a unique mechanism.
- This study reports on the *in vitro* activity of gepotidacin and comparator agents against contemporary UTIs caused by *Escherichia coli* and *Staphylococcus saprophyticus* in patients at European medical centres during 2019–2020 (SENTRY Antimicrobial Surveillance Program).

Materials and Methods

- A total of 1,093 *E. coli* and 82 *S. saprophyticus* isolates were collected from 34 European medical centres located in 17 countries.
- All isolates were recovered from patients with UTIs; 67% percent were from ambulatory, emergency, family practice, and outpatient services.
- Susceptibility testing was performed in a central laboratory (JMI Laboratories) according to Clinical and Laboratory Standards Institute (CLSI) M07 (2018) reference methodology.
- Results were interpreted using European Committee on Antimicrobial Susceptibility Testing (EUCAST) v11.0 (2021).
- Testing of amoxicillin-clavulanic acid was done at a 2:1 ratio and MICs were interpreted using CLSI breakpoints.
- Susceptibility to fosfomycin was determined by agar dilution and was supplemented with glucose-6-phosphate (25 mg/L).
- The extended-spectrum β-lactamase (ESBL) phenotype in *E. coli* was characterized by isolates displaying ceftriaxone MIC values ≥2mg/L.

Gepotidacin demonstrated potent *in vitro* activity against contemporary *E. coli*, including ESBL-producing isolates, and *S. saprophyticus* isolates from European patients with UTIs.

Table 1 Activity of gepotidacin and comparators against isolates collected from urinary tract infections in European medical centers

Organism (No of isolates)	MIC (mg/L)			Interpretation[a]		
Antimicrobial agent	MIC_{50}	MIC_{90}	Range	%S	%I[f]	%R
E. coli (1,093)						
Gepotidacin	2	2	0.06 to 32			
Ciprofloxacin	0.015	>4	≤0.002 to >4	74.6	2.5	23.0
Amoxicillin-clavulanic acid[b]	8	16	1 to >32	97.7		2.3
Trimethoprim-sulfamethoxazole	≤0.12	>16	≤0.12 to >16	70.2		29.0
Nitrofurantoin[c]	16	32	≤2 to >128	98.9		1.1
Fosfomycin[d]	0.5	1	≤0.12 to >256	97.1		2.9
Nitroxoline 30 µg disk[c]	—	—	—	100.0		0.0
Mecillinam[d]	0.5	4	0.06 to >32	93.8		6.2
Meropenem[e]	≤0.015	0.03	≤0.015 to 0.5	100.0	0.0	0.0
S. saprophyticus (82)						
Gepotidacin	0.06	0.12	≤0.03 to 0.12			
Ciprofloxacin	0.25	0.5	0.25 to 0.5		100.0	0.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 to >16	97.6	1.2	1.2
Nitrofurantoin[g]	16	16	4 to 32	100.0		0.0
Fosfomycin[h]	64	>256	32 to >256	—		—

a Interpretations per EUCAST guidelines (2021).
b Using CLSI breakpoints; tested in a 2:1 ratio.
c Uncomplicated UTI only, E.coli.
d Oral breakpoints for uncomplicated UTI only, E. coli; tested by agar dilution.
e For indications other than meningitis.
f I – Susceptible, Increased exposure.
g Uncomplicated UTI only, Staphylococcus saprophyticus.
h No oral breakpoints; isolates may be reported as R without prior testing.

Poster #02122
31st European Congress of Clinical Microbiology & Infectious Diseases (ECCMID) 9–12 July 2021
Hybrid Meeting | Vienna, Austria and Online

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Results

- Gepotidacin ($MIC_{50/90}$, 2/2 mg/L) was active against 1,093 *E. coli* isolates (Table 1).
  - 97.4% of all observed gepotidacin MICs were ≤4 mg/L.
  - Susceptibility rates of ciprofloxacin ($MIC_{50/90}$, 0.015/ >4 mg/L), amoxicillin-clavulanate ($MIC_{50/90}$, 8/16 mg/L), and trimethoprim-sulfamethoxazole (TMP-SMX; $MIC_{50/90}$, ≤0.12/ >16 mg/L) were 74.7%, 78.0%, and 70.2% respectively.
  - Higher susceptibility was observed for fosfomycin ($MIC_{50/90}$, 0.5/1 mg/L; 97.1%S), nitrofurantoin ($MIC_{50/90}$, 16/32 mg/L; 98.9%S), meropenem ($MIC_{50/90}$, ≤0.015/0.03 mg/L; 100%S), mecillinam ($MIC_{50/90}$, 0.5/4 mg/L; 93.8%S), and nitroxoline (100%S).
- An ESBL phenotype was observed in 14.9% of *E. coli* isolates (Table 2).
  - Gepotidacin ($MIC_{50/90}$, 2/4 µg/mL) remained active against these isolates.
  - Activities of the oral agents, ciprofloxacin (MIC_{90}, >4 mg/L; 22.7% susceptible) and trimethoprim/sulfamethoxazole (MIC_{90} >16 mg/L; 38.7% susceptible), were limited.
  - Nitrofurantoin, fosfomycin, nitroxoline, and mecillinam retained activity against these isolates (%S≥93.9%)

Table 2 Activity of gepotidacin and comparators against 163 ESBL *E. coli*

Organism (No of isolates)	MIC (mg/L)			Interpretation[a]		
Antimicrobial agent	MIC_{50}	MIC_{90}	Range	%S	%I[f]	%R
Gepotidacin	2	4	0.06 to 16			
Ciprofloxacin	>4	>4	0.004 to >4	22.7	4.3	73.0
Amoxicillin-clavulanic acid[b]	8	32	4 to >32	51.5	34.4	14.1
Trimethoprim-sulfamethoxazole	>4	>4	≤0.12 to >4	38.7	1.2	60.1
Nitrofurantoin[c]	16	32	4 to >128	96.9		3.1
Fosfomycin[d]	0.5	2	0.25 to >256	93.9		6.1
Nitroxoline 30 µg disk[c]	—	—	—	100.0		0.0
Mecillinam[d]	1	4	0.12 to >32	96.9		3.1
Meropenem[e]	0.03	0.03	≤0.015 to 0.5	100.0	0.0	0.0

a Interpretations per EUCAST guidelines (2021).
b Using CLSI breakpoints; tested in a 2:1 ratio.
c Uncomplicated UTI only, E.coli.
d Oral breakpoints for uncomplicated UTI only, E. coli; tested by agar dilution.
e For indications other than meningitis.
f I – Susceptible, Increased exposure.

- Gepotidacin ($MIC_{50/90}$, 0.06/0.12 mg/L) inhibited all 82 *S. saprophyticus* isolates at ≤0.12 mg/L (Table 1).
- Susceptibility of *S. saprophyticus* isolates to trimethoprim/sulfamethoxazole or nitrofurantoin was ≥97.6% while fosfomycin showed little activity ($MIC_{50/90}$, 64/ >256 mg/L).

Disclosures

This study at JMI Laboratories was supported by GlaxoSmithKline. JMI Laboratories received compensation fees for services in relation to preparing the poster.

Acknowledgments

This project has been funded in whole or in part with Federal funds from the Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority, under OTA Agreement No. HHSO100201300011C.

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