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Digital poster

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In vitro Activity of Gepotidacin and Comparator Agents Against a Collection of *Klebsiella pneumoniae* Urine Isolates Collected from Europe during 2019–2022

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

[1] S. J. Ryan Arends, [2] R. Kapoor, [3] D. Torumkuney, [1] R.E. Mendes

[1] Element Iowa City (JMI Laboratories), North Liberty, Iowa, USA; [2] GSK, Collegeville, PA, USA; [3] GSK, Brentford, Middlesex, UK

Introduction

- Gepotidacin is a novel, bactericidal, first-in-class triazaacenaphthylene antibiotic that inhibits bacterial DNA replication by a unique mechanism of action, distinct binding site, and for most pathogens provides a well-balanced inhibition of two different Type II topoisomerase enzymes.
- Gepotidacin is currently under development for the treatment of uncomplicated urinary tract infections (uUTIs) and gonorrhea.
- This study reports on the in vitro activity of gepotidacin and other oral antibiotics tested against contemporary *Klebsiella pneumoniae* clinical isolates collected from patients with UTIs in Europe as part of a gepotidacin uropathogen global surveillance study.

Methods

- A total of 807 *K. pneumoniae* isolates were collected from 38 European medical centres located in 19 countries from 2019–2022.
- All isolates were tested for susceptibility by CLSI methods (CLSI, 2018) at a central laboratory (Element Iowa City).
- MIC results for comparator agents were interpreted per CLSI and EUCAST guidelines (CLSI, 2023; EUCAST, 2023) to determine % of susceptible (S), intermediate (I), and resistant (R) isolates.
  - Amoxicillin-clavulanic acid was tested at the CLSI-recommended 2:1 ratio and therefore results were interpreted by CLSI breakpoints.
- The extended-spectrum β-lactamase (ESBL) phenotype in K. pneumoniae was characterized as isolates displaying aztreonam, ceftazidime, or ceftriaxone MIC values ≥ 2 mg/L.
- MIC results for oral antibiotics licensed for the treatment of uUTI, multidrug-resistant (MDR), and ESBL subsets were interpreted per EUCAST criteria to identify not susceptible (NS) subsets.
- The MDR phenotype was defined for *K. pneumoniae* as described by Magiorakos et al. (2012) as having a EUCAST-not susceptible phenotype to 3 or more drug classes. Data was not reported for all drugs utilized in the SENTRY program MDR classification.

Results

- Gepotidacin displayed activity against 807 *K. pneumoniae* isolates (Table 1).
  - An $MIC_{50/90}$ of 4/16 mg/L was observed.
  - 91.6% of all observed gepotidacin MICs were ≤16 mg/L.
- Susceptibility rates for all oral comparators tested were below 88% (Table 1).
  - Amoxicillin-clavulanic acid (63.3% S by CLSI; $MIC_{50/90}$, 4/>32 mg/L)
  - Cefadroxil (30µg disk) (61.6% S by EUCAST)
  - Ciprofloxacin (60.2% S; $MIC_{50/90}$, 0.03/>4 mg/L)
  - Mecillinam (87.2% S by EUCAST; $MIC_{50/90}$, 0.5/32 mg/L)
  - Trimethoprim-sulfamethoxazole (61.2% S; $MIC_{50/90}$, 0.25/>4 mg/L)
- Gepotidacin maintained similar MIC_{50} (ranging from 4 – 8 mg/L) and MIC_{90} values (ranging from 16 – 32 mg/L) against drug-resistant subsets (Table 2).
- Gepotidacin remained active against the 40.6% or 25.9% of *K. pneumoniae* isolates that displayed an ESBL or MDR phenotypes, respectively, with observed $MIC_{50/90}$ values of 8/32 mg/L for both (Table 2).

Table 1: **Activity of gepotidacin and other oral agents tested against *K. pneumoniae* UTI isolates collected from medical centers in Europe during 2019–2022**

Organism (No. isolates)	mg/L			EUCAST[a]			CLSI[a]		
Antimicrobial agent	MIC_{50}	MIC_{90}	MIC range	%S	%I	%R	%S	%I	%R
K. pneumoniae (807)									
Gepotidacin	4	16	0.5 to >64	[b]			[b]		
Ampicillin	>64	>64	≤1 to >64	0.9	-	99.1	0.0 [c]	0.0	45.0
Amoxicillin-clavulanic acid[d]	4	>32	0.5 to >32				63.3	9.9	5.9
Cefadroxil[f]	-	-	-	61.6[e]	-	38.4	[b]		
Ciprofloxacin	0.03	>4	0.004 to >4	60.2 [g]	7.4	32.3	60.2	0.2	0.8
Mecillinam[h]	0.5	32	0.06 to >32	87.2[e]	-	12.8	[b]	1.3	16.2
Trimethoprim-sulfamethoxazole	0.25	>4	≤0.12 to >4	61.2	1.4	37.4	61.2	1.5	0.0

[a] Interpretations per CLSI (2023) and EUCAST (2024) guidelines.
[b] Breakpoints not established
[c] Intrinsic resistance.
[d] Tested in CLSI recommended 2:1 ratio; only CLSI breakpoints applied.
[e] Using uncomplicated UTI only breakpoints.
[f] Tested by disk diffusion.
[g] Indications other than meningitidis.
[h] Tested by agar dilution.

Table 2: **Frequency distribution of gepotidacin MIC values for *K. pneumoniae* isolate subsets from Europe with resistance to oral agents in 2019–2022**

Organism (No. isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of:									Gepotidacin	
Not suceptible subset [a]	≤0.5	1	2	4	8	16	32	64	>64	MIC_{50}	MIC_{90}
K. pneumoniae (807)	5 0.6%	28 4.1%	66 12.3%	372 58.4%	169 79.3%	99 91.6%	48 97.5%	18 99.8%	2 100%	4	16
Ampicillin-NS (800)	4 0.5%	28 4.0%	65 12.1%	367 58.0%	169 79.1%	99 91.5%	48 97.5%	18 99.8%	2 100%	4	16
Amoxicillin-clavulanate-NS [b] (296)	2 0.7%	16 6.1%	25 14.5%	64 36.1%	88 65.9%	54 84.1%	35 95.9%	12 100%		8	32
Cefadroxil-NS [c, d] (310)	3 1.0%	18 6.8%	22 13.9%	62 33.9%	85 61.3%	71 84.2%	33 94.8%	15 99.7%	1 100%	8	32
Fluoroquinolone-NS [e] (321)	4 1.2%	23 8.3%	23 15.3%	40 27.6%	89 54.9%	84 80.7%	43 93.9%	18 99.4%	2 100%	8	32
Mecillinam-NS [c, f] (103)	0 0.0%	7 6.8%	9 15.5%	25 39.8%	28 67.0%	19 85.4%	11 96.1%	4 100%		8	32
Trimethoprim-sulfamethoxazole-NS (313)	2 0.6%	16 5.8%	18 11.5%	71 34.2%	83 60.7%	74 84.3%	33 94.9%	14 99.4%	2 100%	8	32
ESBL (328)	3 0.9%	19 6.7%	22 13.4%	69 34.5%	90 61.9%	74 84.5%	35 95.1%	15 99.7%	1 100%	8	32
MDR (209)	2 1%	14 7.7%	19 16.7%	30 31.1%	62 60.8%	45 82.3%	27 95.2%	10 100%		8	32

ESBL, Extended-spectrum β-lactamases; MDR, multidrug resistance; ND, not determined if n<10; NS; not susceptible
[a] Interpreted by EUCAST breakpoints.
[b] Tested at 2:1 ratio and therefore interpreted by CLSI breakpoints.
[c] Using uncomplicated urinary tract infection only breakpoints.
[d] Tested by disk diffusion.
[e] Indications other than meningitidis.
[f] Tested by agar dilution.

Abbreviations

CLSI, Clinical and Laboratory Standards Institute
ESBL, extended-spectrum β-lactamase
EUCAST, European Committee on Antimicrobial Susceptibility Testing
MDR, multidrug resistance
MIC, Minimal inhibitory concentration
NS, not susceptible
NA, not applicable
ND, not determined
S, susceptible
UTI, urinary tract infection

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Disclosures

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Conclusions

- Gepotidacin demonstrated *in vitro* activity against contemporary *K. pneumoniae* UTI isolates from from Europe.
- This activity remained mostly unaffected by resistance to other oral standard-of-care antibiotics with $MIC_{50/90}$ values within 2-fold of those described for the overall population..
- Almost all oral comparator agents reported against European *K. pneumoniae* UTI isolates had susceptibility rates less than 65%; only mecillinam had a higher susceptibility percentage of 87.2%.

Presenting Author: S. J. Ryan Arends, Ph.D., Ryan.Arends@element.com

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