NEWER ANTIBIOTIC PLAZOMICIN

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Beta lactamase classification

- **Class A**:

KPCs that confer resistance to cephalosporins and to all carbapenems, and extended-spectrum beta-lactamases (ESBLs) that confer resistance to cephalosporins.

- **Class B**

Metallo-beta-lactamases (MBLs), such as NDM, VIM, and IMP, which can lead to resistance to all carbapenems except monobactam.

- **Class C**

AmpC (mostly chromosomal but can also be plasmidal), which confer resistance to cephalosporins.

- **Class D**

OXAs that confer resistance mostly to carbapenems.

	ESBL and AmpC	KPC	OXA-48	MBL	Carbapenem Nonsusceptible *A. baumanii*	Carbapenem Nonsusceptible *P. aeruginosa*
Plazomicin	++	++	++	+/- a	-	-
Eravacycline	++	++	++	+b	++	-
Temocillin	++ (urine breakpoint only)	++ (urine breakpoint only)	-	-	-	-
Cefiderocol	++	++	++	++	++	++
Ceftazidime/avibactam	++	++	++	-	-	+/-
Ceftolozane/tazobactam	++	-	-	-	-	+/- c
Meropenem/vaborbactam	++	++	-	-	?	?
Imipenem/relebactam	++	++	-	-	-	+/- d

Table 1- Possible applications of new antibiotics against Gram-negative bacteria based on resistant mechanisms.

Plazomicin

Plazomicin injection **500 mg/10 mL (50 mg/mL)** is a **single-dose** vial containing plazomicin sulfate equivalent to 500 mg plazomicin free base

Therapeutic class: Semisynthetic aminoglycoside derived from **Sisomicin**

Mechanism of Action: Plazomicin acts by binding to bacterial 30S ribosomal subunit, thereby **inhibiting protein synthesis**

Indication: In patients 18 years of age or older for treatment of cUTI, including pyelonephritis caused by the following susceptible microorganism(s): *E. coli, K. pneumoniae, P. mirabilis, and E. cloacae.*

Ther Adv Infect Dis. 2020 Sep 4;7:2049936120952604. doi: 10.1177/2049936120952604.

Potential Activity Against PBP3 inserts

Antibiotic	Target; Mechanism of Action
Ceftazidime Avibactam	**PBP**/β-lactamase enzyme; Cell wall synthesis inhibition
Meropenem- Vaborbactam	**PBP**/β-lactamase enzyme; Cell wall synthesis inhibition
Cefiderocol	**PBP**; Cell wall synthesis inhibition
Imipenem + Cilistatin/ Relebactam	**PBP**/β-lactamase enzyme; Cell wall synthesis inhibition
Aztreonam –Avibactam	**PBP**/β-lactamase enzyme; Cell wall synthesis inhibition
Plazomicin	**30S ribosomal subunit; Protein synthesis inhibition**

Medicina **2024**, 60, 214. https://doi.org/10.3390/medicina60020214

Spectrum of Activity

Gram negative	Enterobacteriaceae family, such as *E. coli, K. pneumoniae, Enterobacter spp., and Proteus spp*
Gram-positive	*S. aureus*, including MRSA, VRSA, heteroresistant vancomycin-intermediate *S. aureus* and *coagulase-negative staphylococci*
Active against Broad range of	✓ AME producing Enterobacteriaceae, ✓ CRE (MBL, Oxa 48, KPC), ESBL producing Enterobacteriaceae ✓ Colistin resistant Enterobacteriaceae ✓ Aminoglycoside resistant

CLSI 2023 Breakpoints

Pathogen	MIC (mcg/mL)			Disk Diffusion (zone diameter in mm)		
	S	I	R	S	I	R
Enterobacteriaceae	≤2	4	≥8	≥16	14-15	≤13

Plazomicin Dosing

Plazomicin has once-daily dosing, administered through a 30-minute IV infusion[1]

Dosage regimen in adults with CrCl ≥90 mL/min

cUTI Infection	Dosage Regimen[b]	Duration of Treatment
cUTI including Pyelonephritis	15 mg/kg every 24 hours	4 to 7 days[c]

Dosage adjustments may be required based on change in renal function in adults with CrCl <90 mL/min;

Estimated CLcr	Recommended Dosage	Dosing Interval
>60 mL/min	15 mg/kg	q24h
>30 to 60 mL/min	10 mg/kg	q24h
>15 to 30 mL/min	10 mg/kg	q48h

Plazomicin is substantially excreted by kidneys, care should be taken in dose selection, and renal function should be monitored.

Synergistic Bactericidal Activity vs CRE

Key Results

- **Plazomicin (0.5 × MIC)** in combination with colistin or fosfomycin, **synergy was observed as well as a >3 log10 decrease in CFU/mL** at 24 h

- When **1 × MIC of plazomicin** was combined with **colistin, meropenem or fosfomycin, bactericidal and synergistic activity** was observed by 24 h for both isolates

- **Plazomicin alone at 2 × MIC was rapidly bactericidal, achieving a 3 log decrease in CFU/mL by 3 h** of exposure, and the bactericidal activity was **sustained up to the 6 h and 24 h time points** against the two isolates tested

Combination of plazomicin with colistin, meropenem or fosfomycin showed in-vitro synergistic activity against carbapenemase-producing K. pneumoniae isolates despite high MICs to comparator antibiotics

In

Summary

- **Once Daily Dosing** unlike other AGs
- Activity against **resistant pathogens** (**PBP3 inserts, AME producers, ESBL, CRE, Colistin resistant Enterobacteriaceae**)
- Better activity against **CRE & Colistin resistant Enterobacteriaceae** than other AGs
- Proven efficacy in phase III trial - **Noninferior to meropenem**
- Acceptable **tolerability profile** (Less nephrotoxicity than colistin)
- Synergy with meropenem, fosfomycin and colistin in CRE isolates
- WHO has categorized it as **Reserve Antibiotic**
- Useful **targeted therapy for cUTI** and acute pyelonephritis caused by resistant pathogens