

Brand Name: Zemdri

Generic Name: plazomicin

Manufacturer: Achaogen, Inc

Drug Class: aminoglycoside antibacterial

Uses: ¹⁻⁵

- Labeled: treatment of complicated urinary tract infections (cUTI), including pyelonephritis, caused by susceptible *Eschericia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Enterobacter cloacae* in patients 18 years or older.
- Unlabeled: none

Mechanism of Action: ¹ Plazomicin binds the bacterial 30S ribosomal subunit which inhibits protein synthesis. It has concentration dependent bactericidal activity and a post-antibiotic effect ranging from 0.2 to 2.6 hours at 2x MIC against *Enterobacteriaceae*.

Plazomicin has activity against *Eschericia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterobacter cloacae*, *Citrobacter freundii*, *Citrobacter koseri*, *Enterobacter aerogenes*, *Klebsiella oxytoca*, *Morganella morganii*, *Proteus vulgaris*, *Providencia stuartii*, and *Serratia marcescens*.

Pharmacokinetics: ¹

Parameter	Healthy Adult	cUTI Patient
Cmax (mcg/mL)(mean ± SD)	73.7 ± 19.7	51.0 ± 113
Vd (L)(mean ± SD)	17.9 ± 4.8	30.8 ± 12.1
t _{1/2} (h)(mean ± SD)	3.5 ± 0.5	-
Clearance (L/h)(mean ± SD)	4.5 ± 0.9	5.1 ± 2.01
Protein Binding	20%	
Bioavailability	100%	100%

Metabolism: ¹ Does not appear to be metabolized to any appreciable extent.

Elimination: ¹⁻⁵ Primarily excreted by the kidney, 97.5% unchanged.

Efficacy:

Cloutier DJ, Miller LG, Komirenko AS, et al. Evaluate the efficacy and safety of plazomicin compared with meropenem followed by optional oral therapy for the treatment of complicated urinary tract infection. ClinicalTrials.gov. 2018 Aug; Trial NCT02486627

Study design: Randomized, multicenter, multinational, double-blind study

Description of study: A total of 609 patients with complicated urinary tract infection (cUTI) including acute pyelonephritis and who had pyuria and a baseline urine culture were randomized to receive either plazomicin (15 mg/kg) intravenously (IV) once daily for at least 4 days or meropenem (1.0 g) IV every 8 hours for at least 4 days. Both groups were allowed to switch to oral levofloxacin (250 or 500mg for 7-10 days)

following initial IV treatment. Efficacy in the modified intention to treat population was assessed on day 5 and day 17 to determine microbiological eradication ($<10^4$ CFU/mL in urine) and clinical cure. The median treatment duration of intravenous study drug was 6 days for both groups. Treatment success at day 5 for plazomycin (88%) was lower than that of meropenem (91.4%) (-3.4, 95% CI -10.0 to 3.1). However at day 17 (test-of-cure) plazomycin (81.7%) had a higher success rate than meropenem (70.1%) (11.6, 95% CI 2.7 to 20.3). Some *Enterobacteriaceae* isolates were non-susceptible (27%) to gentamicin, or tobramycin, or both.

Limitations: Study participants were overwhelmingly white (99.5%) and had an average age of almost 60 years old. Additionally, a hypothesis of noninferiority or superiority was not assessed and this study has not been published or peer reviewed.

Conclusion: Plazomycin can be effective at curing cUTI, however, its efficacy compared to meropenem cannot be determined because the study was lacking information on the statistical analysis of the treatments.

Cass RT, Brooks CD, Havrilla NA, Tack KJ, Borin MT, Young D, Bruss JB. Pharmacokinetics and safety of single and multiple doses of ACHN-490 injection administered intravenously in healthy subjects. Antimicrob Agents Chemother. 2011 Dec;55(12):5874-80.

Study Design: Randomized, double-blind, placebo-controlled, intent-to-treat protocol

Description of study: This was a combination of two studies in healthy adults assessing safety and pharmacokinetic values. The majority of patients were white males from 20-30 years old. The first study utilized escalating single and multiple doses in a parallel-group design. A total of 39 subjects received either plazomycin (ACHN-490) (30 subjects) or placebo (9 subjects) at 1 mg/kg followed by ascending single dose and multidose cohorts. The second study used the highest dose tolerated from study one and continued it for a longer duration. Subjects received 15 mg/kg for 5 days of active drug (6 subjects) or placebo (2 subjects). Pharmacokinetic values were assessed using blood and urine samples. The mean elimination half-life across all groups ranged from 3 to 4 hours and no drug accumulation was seen after repeated dosing over 5 days.

Safety was assessed by monitoring for adverse effects as well as by performing tests to evaluate vestibular, cochlear, and renal function. None of the subjects discontinued treatment because of adverse effects, auditory studies showed no abnormal results up to 6 months after receipt of plazomycin, and there were no effects on renal function.

Limitations: This study was conducted in healthy patients that were overwhelmingly white males. Pharmacokinetic values may change in patients that are not healthy. Furthermore, urinary tract infections are more common in women, who were underrepresented in this study.

Conclusions: Plazomycin did not cause any serious adverse events, cochlear dysfunction, or renal dysfunction when tested in healthy subjects so it is likely safe. Furthermore, the highest dose tested did not accumulate in the body with repeated doses over 5 days.

Martins AF, Bail L, Ito CAS, da Silva Nogueira K, Dalmolin TV, Martins AS, Rocha JLL, Serio AW, Tuon FF. Antimicrobial activity of plazomicin against Enterobacteriaceae-producing carbapenemases from 50 Brazilian medical centers. *Diagn Microbiol Infect Dis.* 2018 Mar;90(3):228-232.****

Study design: *In vitro* antimicrobial susceptibility study using isolates from patients

Description of study: Isolates of *Enterobacteriaceae* were collected from 50 Brazilian hospitals. The isolates (1 per patient) were from the bloodstream, respiratory tract, cerebrospinal fluid, and other infections. A total of 499 isolates were tested against colistin, tigecyclin, meropenem, amikacin, gentamicin, and plazomicin to determine the minimum inhibitory concentration (MIC). Certain antibiotics were not tested against select isolates because of known resistance. The study found that plazomicin had activity against 87% of isolates at an MIC ≤ 4 mg/L including carbapenemase producing *Enterobacteriaceae* (CPE).

Limitations: This was an *in vitro* study. Although it is promising in that it shows plazomicin has activity certain multidrug resistant bacteria, this study does not prove that plazomicin will be able to treat patients infected with these bacteria or that it is safe for humans at concentrations necessary to produce antibiotic effects. Furthermore it is not clear if plazomicin will penetrate all areas of the body, including cerebral spinal fluid, in order to treat these infections *in vivo*.

Conclusion: Plazomicin was shown to have activity against 87% of isolates tested, including multidrug resistant CPE. However, clinical trials in humans need to be done to determine safety and clinical efficacy in treating these infections *in vivo*.

Denervaud-Tendon V, Poirel L, Connolly LE, Krause KM, Nordmann P. Plazomicin activity against polymyxin-resistant Enterobacteriaceae, including MCR-1-producing isolates. *J Antimicrob Chemother.* 2017 Oct 1;72(10):2787-2791.****

Study design: *In vitro* susceptibility study against colistin-resistant enterobacterial isolates

Description of study: A total of 95 colistin-resistant enterobacterial isolates were collected from 29 hospitals in eight countries (Angola, Colombia, France, Portugal, South Africa, Spain, Switzerland, and Turkey). Those isolates had genetically encoded colistin-resistance mechanisms, intrinsic colistin-resistance, and undefined resistance mechanisms. Isolates were tested for susceptibility against colistin, amikacin, gentamicin, plazomicin, tobramycin, piperacillin/ tazobactam, ceftazidime, ceftriaxone, doripenem, imipenem, meropenem, aztreonam, levofloxacin, tigecycline, and sulfamethoxazole/ trimethoprim. Bacterial susceptibility to plazomicin was assessed based on minimum inhibitory concentrations (MIC). Plazomicin was active against 89.5% of isolates at ≤ 2 mg/L and 93.7% of isolates at ≤ 4 mg/L.

Limitations: This was an *in vitro* study and may not reflect *in vivo* activity. More studies need to be completed in humans demonstrating cures of clinical infection. Additionally, antibiotic resistance patterns are different in different areas.

Conclusion: The results from this study are promising, even *in vitro*, because of the increasing trend of bacterial resistance to current antibiotics. However, these results would need to be duplicated in humans to show plazomicin as a safe and effective clinical treatment.

Contraindications¹⁻⁵: Patients with known hypersensitivity to any aminoglycoside

Precautions:¹⁻⁵ Black box warning for: nephrotoxicity, ototoxicity, neuromuscular blockade, and fetal harm. Also hypersensitivity reactions (including anaphylaxis), *Clostridium difficile* associated diarrhea, and development of drug resistant bacteria

Adverse effects:¹⁻⁵

Common: Decreased renal function (3.6%), diarrhea (2.3%), hypertension (2.3%), headache (1.3%), nausea/ vomiting (1.3%), constipation, gastritis, ALT increase, hypokalemia, dizziness, hematuria, dyspnea

Severe: Nephrotoxicity (7%), ototoxicity (2.2%)

Drug Interactions¹⁻⁵: No drug interactions are known. *In vitro* studies suggest plazomicin does not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, or 3A5. It also does not induce CYP1A2, 2B6, or 3A4. Furthermore plazomicin is not a substrate of P-gp or BCRP transporters and it does not inhibit P-gp, BCRP, BSEP, MRP2, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, or OCT2. Plazomicin did inhibit MATE1 and MATE2-K renal transporters *in vitro*¹ which transport drugs including metformin, cimetidine, cephalixin, oxaliplatin, and acyclovir⁶.

Dosing/Administration:¹⁻⁵

In adults with CrCl_r ≥ 90 mL/min: 15 mg/kg intravenous infusion over 30 minutes every 24 hours for 4 to 7 days. No therapeutic drug monitoring needed.

For patients with CrCl_r <90 mL/min and ≥15 mL/min: therapeutic drug monitoring to maintain plasma trough concentrations below 3 mcg/mL. Measure plasma concentrations ≈30 minutes before administration of second dose. Adjustment involves extending the dosing interval by 1.5 fold for patients with plasma trough concentrations ≥3 mcg/mL.

Geriatric dose: according to renal function and therapeutic drug monitoring.

Pediatric dose: not available

Hepatic impairment dose: no adjustment needed

Renal impairment dose:

Estimated CrCl _r (mL/min)	Dosage	Dosing Interval
≥60 - <90	15 mg/kg	Every 24 hours
≥30 - <60	10 mg/kg	Every 24 hours
≥15 - <30	10 mg/kg	Every 48 hours
Insufficient evidence to recommend dosing in patients with CrCl _r <15 mL/min or patients on renal replacement therapy		

Use in special circumstances:

Pregnancy – Should be avoided in pregnancy. Aminoglycosides can cause fetal harm when used in pregnancy, however, no data on plazomicin specifically in pregnant women exists.¹⁻⁵

Lactation - There is no data on the presence of plazomicin in breast milk nor on its effect on infants or milk production.¹⁻⁵

Obesity - For patients with total body weight (TBW) \geq 25% of ideal body weight (IBW) use adjusted body weight (ABW) for dosing.^{4,5}

Conclusion:

Plazomicin is a new aminoglycoside antibiotic that should be reserved for use until all other treatment options have been exhausted. The main advantage with plazomicin is the activity against microbes including multidrug resistant *E.coli*, *K.pneumoniae*, *P.mirabilis*, and *E.cloacae* that may otherwise be resistant to current antibiotic therapy. When used intravenously in humans, plazomicin has been shown to eradicate bacterial infection and resolve clinical symptoms of complicated urinary tract infections, however, its efficacy compared to current therapy was not determined. Studies assessing the efficacy of plazomicin in other types of infections are lacking. There is evidence from *in vitro* studies that plazomicin may have activity against antibiotic resistant microbes including carbapenemase producing *Enterobacteriaceae* and colistin resistant bacteria but these results need to be confirmed in humans. Like many antibiotics, plazomicin carries the risk of *Clostridium difficile* infection. Furthermore plazomicin has a black box warning for nephrotoxicity, ototoxicity, neuromuscular blockade, and fetal harm. These negative outcomes need to be taken into account when considering the potential risks and benefits that a patient could have. Due to the limited studies and clinical experience with plazomicin at this time, it should be reserved for patients who have few or no other treatment options.

Recommended References:

1. Product Information: ZEMDRI™ intravenous injection, plazomicin intravenous injection. Achaogen Inc (per FDA), South San Francisco, CA, 2018.
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4. Plazomicin. Lexi-Drugs [database online]. Lexi-Comp, Inc; Last updated September 11, 2018. Accessed September 24, 2018
5. Plazomicin injection. Facts & Comparisons 4.0 Online [Internet database]. Wolters Kluwer. Available at: <http://online.factsandcomparisons.com>. Accessed September 24, 2018.
6. Tanihara Y, Masuda S, Sato T, Katsura T, Ogawa O, Inui K. Substrate specificity of MATE1 and MATE2-K, human multidrug and toxin extrusions/H(+)-organic cation antiporters. *Biochem Pharmacol*. 2007 Jul 15;74(2):359-71.
7. Zemdri.com. Achagon 2018
8. U.S. National Library of Medicine. 8600 Rockville Pike, Bethesda, MD 20894. Available at: Clinicaltrials.gov

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