

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210303Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Reviewer Name(s)	Ingrid N. Chapman, Pharm.D., BCPS
Team Leader	Elizabeth Everhart, MSN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	06/25/2018
Subject	Evaluation of Need for a REMS
Established Name	Plazomicin
Trade Name	Zemdri
Name of Applicant	Achaogen Inc
Therapeutic Class	Aminoglycosides
Formulation(s)	Solution for injection
Dosing Regimen	15 mg/kg IV every 24 hours

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Zemdri (plazomicin), an aminoglycoside, is necessary to ensure the benefits outweigh its risks. Achaogen Inc. submitted a New Drug Application (NDA 210303) with the proposed indication:

- As a single agent in patients 18 years or older for the treatment of complicated urinary tract infections (cUTI) including pyelonephritis caused by the following susceptible microorganism(s): *Escherichia coli* (including cases with concurrent bacteremia), *Klebsiella pneumoniae*, *Proteus* spp. (including *P. mirabilis* and *P. vulgaris*), and *Enterobacter cloacae*.
- In patients 18 years or older for the treatment of bloodstream infections (BSI) caused by the following susceptible microorganism(s): *Klebsiella pneumoniae* and *Escherichia coli*

The serious risks associated with plazomicin include nephrotoxicity, ototoxicity, neuromuscular blockade toxicity, and fetal harm. These serious risks are similar to those of other approved aminoglycosides including gentamicin, tobramycin, and amikacin. The applicant did not submit a proposed REMS or risk management plan with this application. If approved, the labeling will communicate the serious risks of plazomicin and the management of those risks with a Boxed Warning. The Warnings and Precautions section of the proposed label also addresses the risks of hypersensitivity reactions and *clostridium difficile*-associated diarrhea. DRISK and the Division of Anti-infective Products (DAIP) agree that a REMS is not needed to ensure the benefits of plazomicin outweigh its risks.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Zemdri (plazomicin) is necessary to ensure the benefits outweigh its risks. Achaogen Inc. submitted a New Drug Application (NDA 210303) for plazomicin with the proposed indication:

- As a single agent in patients 18 years or older for the treatment of complicated urinary tract infections (cUTI) including pyelonephritis caused by the following susceptible microorganism(s): *Escherichia coli* (including cases with concurrent bacteremia), *Klebsiella pneumoniae*, *Proteus* spp. (including *P. mirabilis* and *P. vulgaris*), and *Enterobacter cloacae*.
- In patients 18 years or older for the treatment of bloodstream infections (BSI) caused by the following susceptible microorganism(s): *Klebsiella pneumoniae* and *Escherichia coli*

This application is under review in the Division of Anti-infective Products (DAIP). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Zemdri (plazomicin), a new molecular entity,^a is an aminoglycoside proposed:

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

- As a single agent in patients 18 years or older for the treatment of complicated urinary tract infections (cUTI) including pyelonephritis caused by the following susceptible microorganism(s): *Escherichia coli* (including cases with concurrent bacteremia), *Klebsiella pneumoniae*, *Proteus* spp. (including *P. mirabilis* and *P. vulgaris*), and *Enterobacter cloacae*.
- In patients 18 years or older for the treatment of bloodstream infections (BSI) caused by the following susceptible microorganism(s): *Klebsiella pneumoniae* and *Escherichia coli*

Plazomicin is proposed as a 500 mg ((b) (4) mg/mL) sterile solution for intravenous administration. The recommended dose is 15 mg/kg IV every 24 hours. The duration of therapy should be guided by the severity and site of infection and the patient's clinical and bacteriological progress.^{1b} Plazomicin is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for [Application/Number] relevant to this review:

- 12/19/2008: IND 102563 submission received for plazomicin
- 08/15/2015: Fast Track Designation granted to plazomicin under IND 102563
- 12/18/2014: Qualified Infectious Disease Product (QIDP) Designation granted to plazomicin under IND 102563
- 05/17/2017: Breakthrough Therapy Designation granted to plazomicin under IND 102563
- 10/25/2017: NDA 210303 submission received for plazomicin
- 03/19/2018: A Post Mid-cycle meeting was held between the FDA and the applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for plazomicin.
- 05/02/2018: Meeting of the Antimicrobial Drugs Advisory Committee was convened to discuss whether the applicant provided substantial evidence of the safety and effectiveness of plazomicin for the treatment of cUTI and/or BSIs in patients with limited or no treatment options. The AC voted in favor of the cUTI indication and voted against the indication for BSIs.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

3.1.1 Complicated Urinary Tract Infections

Urinary tract infections (UTIs) are some of the most common bacterial infections affecting approximately 150 million people worldwide.^{c,2} Complicated UTIs (cUTIs) are UTIs with metabolic, functional or structural abnormalities that compromise the urinary tract or host defence.^{2,3} Examples include diabetes, pregnancy, immunosuppression, catheters, and abscess. cUTIs are life-threatening

^b Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug.

^c Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.

and a major cause of bacteremia with high mortality rates of 20-40%.^{d,4} The usual pathogens in community acquired UTIs include *E. coli* or other Enterobacteriaceae. In hospitalized or institutionalized patients, enterococci may be implicated.⁵

3.1.2 Bloodstream Infections

Bloodstream infections (BSIs) (also known as bacteremia) are serious infections that increase mortality rate, prolong patient stays in intensive care units/hospitals, and generate substantial costs. BSIs represent 15% of all nosocomial infections.⁶ In 2008, BSIs were ranked as the 11th leading cause of death in the U.S. accounting for approximately 36,000 deaths.⁷ An estimated 71,900 healthcare associated BSIs occurred in acute care hospitals in 2011.⁸ Community-acquired BSI are often due to *Streptococcus pneumoniae* and *Staphylococcus aureus* for Gram positive, and *Escherichia coli* for Gram negative.⁹ Multidrug resistant organisms (MDROs) must be considered in the healthcare setting.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Treatment of BSI and cUTIs is dependent upon many factors including pathogen identification, the site of infection, host factors, severity of illness, and local antibiotic resistance. For cUTI, non-pharmacologic treatment consists of hydration, relief of urinary tract obstruction, and/or removal of foreign body (e.g. catheter). BSIs usually occur in hospitalized patients which necessitates pharmacologic therapy with an appropriate intravenous antimicrobial in a timely manner.

The mainstay of pharmacologic therapy for both cUTIs and BSIs consist of broad spectrum antibiotics with de-escalation once cultures and sensitives are available. Empiric therapy for cUTIs may include oral or intravenous therapy with fluoroquinolones, cephalosporins, penicillins, extended-spectrum penicillins, carbapenems, and aminoglycosides.⁵ Hospitalized or institutionalized patients with a cUTI may require empiric therapy with ampicillin or vancomycin for enterococci.

4 Benefit Assessment

4.1 COMPLICATED UTI INCLUDING PYELONEPHRITIS

Study ACHN-490-009 (study 009; NCT02486627) was a phase 3, randomized, double-blind study in 609 patients with a clinical diagnosis of cUTI including acute pyelonephritis (AP) requiring at least 4 days of therapy. The patients were randomized 1:1 to either plazomicin 15 mg/kg IV once daily (n = 306) followed 8 and 16 hours later by matching placebo or meropenem 1 gram IV every 8 hours (n = 303). After 4 days, patients were permitted to switch to open-label oral levofloxacin (250 mg or 500 mg once daily). A maximum of 7 days of blinded IV study drug was allowed after which patients would switch to oral therapy or be removed from the study to complete further treatment. The co-primary endpoints were composite microbiological eradication and clinical cure rate in the microbiological modified intent-to-treat (mMITT) population at the Day 5 and test of cure (TOC) visits. The term co-primary for this study meant that noninferiority had to be shown for the primary endpoint at both Day 5 and TOC.

^d Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

Approximately 75% of the randomized patients completed study treatment with plazomicin (n = 229) and meropenem (n = 227). The mMITT population included 388 patients (plazomicin group = 191 and meropenem group = 197). Results showed the composite cure rate of microbiological response and clinical response at Day 5 was 168/191 (88.0%) in the plazomicin group compared to 180/197 (91.4%) in the meropenem group, with a treatment difference (plazomicin - meropenem) of -3.4 and a 95% CI of (-10.0, 3.1). At TOC, the response rates were 156/191 (81.7%) and 138/197 (70.1%) for the plazomicin group and meropenem group, respectively, with a treatment difference of 11.6 and a 95% CI of (2.7, 20.3). The clinical reviewer stated that the results support the conclusion that plazomicin is non-inferior to meropenem for the treatment of cUTI including AP.¹⁰

4.2 BLOODSTREAM INFECTIONS

Originally, Study ACHN-490-007 (study 007; NCT01970371) was a phase 3, randomized, open-label superiority cohort study comparing the efficacy and safety of plazomicin compared to colistin for the treatment of patients with a BSI or hospital-acquired bacterial pneumoniae (HABP)/ventilator-associated bacterial pneumoniae (VABP) due to carbapenem-resistant Enterobacteriaceae (CRE). The study protocol was amended to allow enrollment of patients into two cohorts. Patients ineligible to enroll in Cohort 1 could enroll in Cohort 2.

- Cohort 1 (n = 39) was a randomized (1:1), comparator-controlled cohort of patients with a BSI or HABP/VABP due to CRE comparing the efficacy and safety of plazomicin (plus meropenem or tigecycline) to colistin (plus meropenem or tigecycline).
- Cohort 2 (n = 30) was a single-arm uncontrolled cohort of patients with a BSI, HABP/VABP, cUTI, or AP due to CRE. For BSI or HABP/VABP, adjunctive antibiotic therapy with at least one agent with activity against Enterobacteriaceae was added to plazomicin by the investigator. For cUTI, plazomicin was used as monotherapy with the option to switch to oral therapy on or after Day 5.

For both cohorts, plazomicin was dosed at 15 mg/kg IV once daily for 7 to 14 days (cUTI or AP; 4 – 7 days). Dosing was based on renal function (creatinine clearance) or the type of renal replacement therapy. Dose modifications were based on plazomicin therapeutic drug management (TDM). For Cohort 1, colistin was dosed a colistimethate sodium 5 mg/kg IV once (loading dose) followed by 5 mg/kg IV every 8 hours or every 12 hours with dose adjustments for renal function. Tigecycline was dosed at 100 mg IV once (loading dose) followed by 50 mg IV every 12 hours with dose adjustments for hepatic function. Meropenem was dosed at 2 grams IV every 8 hours with dose adjustments for renal function.

For Cohort 1, the primary endpoints were all-cause mortality (ACM) or significant disease-related complications (SRDCs) and ACM at Day 28. ACM at Day 28 was 7.1% (1/14) for plazomicin compared to 6% (6/15) for colistin. ACM or SRDCs at Day 28 was 14.3% (2/14) for plazomicin compared to 53.3% (8/15) for colistin. The difference observed between groups represents a 39% absolute and 73% relative reduction for plazomicin compared with colistin. For Cohort 2, the ACM rate at Day 28 was 14.3% (2/14) and the ACM or SRDC at Day 28 was 35.7% (5/14).¹¹ (b) (4)

(b) (4)

The BSI indication will be receiving a complete response (CR).

5 Risk Assessment & Safe-Use Conditions^e

The overall evaluation of safety is focused on the plazomicin Phase 2 and Phase 3 studies.¹² Study ACHN-490-002 (NCT01096849) was pooled with study 009 as they both were conducted in adults patients with cUTI including AP. Study 007, cohort 1, provided the primary data to support the safety of plazomicin in patients with BSI. The serious adverse reactions (referred to as serious risks) determined to be associated with plazomicin are nephrotoxicity, ototoxicity, neuromuscular blockade, and fetal harm.^f Additional risks include hypersensitivity reactions and *clostridium difficile*-associated diarrhea. These risks are discussed in the sections below along with the deaths that occurred.

5.1 NEPHROTOXICITY

In the pooled cUTI/AP studies, 13/377 (3.4%) patients receiving plazomicin experienced treatment emergent adverse events (TEAEs) associated with decreased renal function compared to 4/345 (1.2%) in the comparator groups. Increases in serum creatinine \geq 0.5 mg/dL above baseline occurred in 6.7% of patients in the plazomicin group compared to 3.8% in the comparator groups.

In study 007 (cohort 1), in patients with BSI, 33.3% of patients receiving plazomicin experienced TEAEs associated with renal function compared to 52.4% receiving colistin. Increases in serum creatinine \geq 0.5 mg/dL above baseline occurred in 16.7% of patients in the plazomicin group compared to 50% in patients receiving colistin.

The proposed label includes nephrotoxicity in a Boxed Warning and states, “Nephrotoxicity has been reported with (b) (4) Zemdri. The risk of nephrotoxicity is greater in patients with impaired renal function, those receiving (b) (4) concomitant nephrotoxic medications. (b) (4)

^e Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

^f Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

5.2 OTOTOXICITY

In the pooled cUTI studies, 3 mild TEAEs associated with ototoxicity (cochlear or vestibular function) occurred in patients receiving plazomicin compared to 2 TEAEs in the comparator group. No TEAEs associated with ototoxicity were reported in cohort 1 of Study 007 in patients with BSI.

The proposed label includes ototoxicity in a Boxed Warning and states, "Ototoxicity, manifested as hearing loss, tinnitus, and/or vertigo, has been reported [REDACTED] (b) (4). Symptoms may be irreversible and may not become evident until after completion of therapy."

5.3 NEUROMUSCULAR BLOCKADE

Neuromuscular blockade leading to respiratory depression, a rare but potentially serious risk associated with the aminoglycoside class, has not been observed in clinical studies of plazomicin conducted to date.¹² The proposed label includes neuromuscular blockade toxicity in a Boxed Warning and states, "Aminoglycosides have been associated with neuromuscular blockade. [REDACTED] (b) (4)

[REDACTED]
[REDACTED] Monitor for adverse reactions associated with neuromuscular blockade."

5.4 FETAL HARM

In nonclinical studies in pregnant animals, plazomicin was not teratogenic and did not affect fetal viability or growth in rats or rabbits at up to 0.8-fold and 2.5-fold the human area under the curve at the clinical dose of 15 mg/kg/day.¹² One patient in study 002 experienced a serious adverse event (SAE) of spontaneous abortion after receiving 5 doses of plazomicin 15 mg/kg. The SAE was determined to be severe and not related to plazomicin. The proposed label includes fetal harm in a Boxed Warning and states, "Aminoglycosides can cause fetal harm when administered to a pregnant woman." This risk is also addressed in the Warnings and Precautions section of the proposed label.

5.5 HYPERSENSITIVITY REACTIONS

No cases of anaphylaxis or other severe hypersensitivity or allergic reactions were reported in patients treated with plazomicin.¹² However, hypersensitivity reactions have been reported for other aminoglycosides. The Warnings and Precautions section of the proposed label advises if an allergic reaction occurs, discontinue plazomicin.¹

5.6 CLOSTRIDIUM DIFFICILE-ASSOCIATED DIARRHEA

No cases of *clostridium difficile*-associated diarrhea were reported in plazomicin treated patients.¹² However, *clostridium difficile*-associated diarrhea has been reported for nearly all systemic antibacterial drugs. The Warnings and Precautions section of the proposed label advises to evaluate if diarrhea occurs.¹

5.7 DEATHS

One death occurred in the cUTI studies. The patient received plazomicin and died on Study Day 18 due to metastatic uterine cancer. The death was considered unrelated to plazomicin. In Cohort 1 of the BSI Study, 007, 8 (44.4%) deaths occurred in the plazomicin group compared to 13 (61.9%) in the colistin

group. The deaths in the plazomicin group were attributed to septic shock (n = 3), cardiac arrest, cardiorespiratory arrest, lung infection, pneumonia, and pneumonitis chemical (each: n = 1). These fatal SAEs were determined not related to plazomicin.

6 Expected Postmarket Use

Plazomicin will be primarily prescribed in the inpatient setting and the likely prescribers will be infectious diseases providers, critical care providers, and hospitalists. These providers are likely to be familiar with the management of adverse events associated with aminoglycosides including gentamicin, tobramycin, and amikacin. The proposed draft labeling currently addresses the associated serious risks and management of nephrotoxicity, ototoxicity, neuromuscular blockade, and fetal harm in a Boxed Warning. These risks are also addressed in the label of other injectable aminoglycosides as a Boxed Warnings or in the Pregnancy Considerations section.¹³ See Table 1 in the appendix for additional details.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities beyond labeling and routine pharmacovigilance for plazomicin.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of plazomicin for the cUTI indication based on the efficacy and safety information currently available. The BSI indication will be receiving a complete response. Infections due to gram negative bacteria including cUTI and BSI are potentially life-threatening. This is of particular importance when these infections occur in hospitalized patients with MDR pathogens. Treatment is determined by the patient's status, comorbidities, and local drug resistance rates. Plazomicin offers an additional option to treat gram negative infections caused by the following susceptible microorganism(s): *Escherichia coli* (including cases with concurrent bacteremia), *Klebsiella pneumoniae*, *Proteus* spp. (including *P. mirabilis* and *P. vulgaris*), and *Enterobactercloacae*.

The serious risks associated with plazomicin are nephrotoxicity, ototoxicity, neuromuscular blockade, and fetal harm. The healthcare providers prescribing plazomicin should be familiar with managing these risks as they are well known to be associated with aminoglycosides. The labeling will be used to communicate these risks. DRISK recommends that, should plazomicin be approved, a REMS is not necessary to ensure its benefits outweigh its risks for the cUTI including AP.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable and therefore, a REMS is not necessary for plazomicin to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 REFERENCES

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10.2 AMINOGLYCOSIDE RISK MANAGEMENT APPROACHES¹³

	Important Safety and Tolerability Issues	Risk Management Approaches
Streptomycin for injection	Neurotoxicity including (disturbances of vestibular and cochlear function, optic nerve dysfunction, peripheral neuritis, arachnoiditis, and encephalopathy) Nephrotoxicity Neuromuscular Blockade	Labeling – Boxed Warning
	Fetal Harm	Labeling – Pregnancy Considerations
Gentamicin for injection	Neurotoxicity (manifested by ototoxicity) Nephrotoxicity Fetal Harm	Labeling – Boxed Warning
Tobramycin for injection	Ototoxicity Nephrotoxicity Fetal Harm	Labeling – Boxed Warning
	Neuromuscular Blockade	Labeling – Warnings and Precautions
Amikacin for injection	Ototoxicity Nephrotoxicity Neuromuscular Blockade	Labeling – Boxed Warning
	Fetal Harm	Labeling – Pregnancy Considerations

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/s/

INGRID N CHAPMAN
06/25/2018

JAMIE C WILKINS PARKER on behalf of CYNTHIA L LACIVITA
06/25/2018