

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210303Orig1s000

SUMMARY REVIEW

**Cross-Discipline Team Leader, Division Director and Office Director
Summary Review for Regulatory Action**

Date	(electronic stamp)
From	Sumathi Nambiar MD MPH and Edward Cox MD MPH
Subject	Division Director Summary Review
NDA #	210303
Applicant	Achaogen, Inc.
Date of Submission	October 27, 2017
PDUFA Goal Date	June 25, 2018
Proprietary Name / Non-Proprietary Name	ZEMDRI/Plazomicin
Dosage Form / Strength	Injection; 500 mg/10 mL vial
Applicant Proposed Indications	Complicated urinary tract infections (cUTI) Bloodstream infections (BSI)
Action for NME	Approval for the cUTI indication Complete Response for the BSI indication
Approved Indication	Treatment of patients 18 years of age or older with cUTI including pyelonephritis As only limited clinical safety and efficacy data are available, reserve ZEMDRI for use in patients who have limited or no alternative treatment options.

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Shrimant Mishra MD MPH
Statistical Review	Daniel Rubin PhD and Hengrui Sun DrPH
Pharmacology Toxicology Review	Amy Ellis PhD
OPQ Review	Dorota Matecka PhD (ATL)
Microbiology Review	Simone Shurland PhD
Clinical Pharmacology Review	Kunyi Wu PharmD and Luning (Ada) Zhuang PhD
OPDP	David Foss
OSI	John Lee MD
OSE/DMEPA	Deborah Myers RPh, MBA
OSE/DRISK	Ingrid Bergman PharmD

OND=Office of New Drugs

OPQ=Office of Pharmaceutical Quality

ATL=Application Technical Lead

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Plazomicin (ZEMDRI) for injection is an aminoglycoside antibacterial drug. It is active in vitro against members of the Enterobacteriaceae class, including *Escherichia coli* and *Klebsiella pneumoniae*. Plazomicin has no in vitro activity against streptococci (including *Streptococcus pneumoniae*), enterococci (including *Enterococcus faecalis*, *E. faecium*), anaerobes, *Stenotrophomonas maltophilia* and *Acinetobacter* spp and variable activity against *Pseudomonas aeruginosa*.

In NDA 210303, the Applicant is seeking the approval of plazomicin for two indications, one for the treatment of complicated urinary tract infections (cUTI) and the second for the treatment of bloodstream infections. [REDACTED] (b) (4)

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The Applicant requested review of the BSI indication under section 506(h) of the Federal Food, Drug and Cosmetic Act (FD&C Act), the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD).

Efficacy: Assessment of efficacy for each indication is summarized below:

Complicated Urinary Tract Infections (cUTI):

The Applicant conducted one double-blind noninferiority (NI) Phase 3 trial in adults with cUTI, including acute pyelonephritis where plazomicin was compared to meropenem with an option to switch to oral therapy after at least 5 days of intravenous (IV) treatment. The Applicant also conducted a dose-ranging Phase 2 trial in patients with cUTI (Study 002) with levofloxacin as the comparator. One adequate and well-controlled trial, along with supportive information was considered adequate to demonstrate the efficacy of plazomicin for the treatment of cUTI, including pyelonephritis based on the potential for plazomicin to address an unmet medical need and labeling that will include limited use language. Supportive evidence for the single Phase 3 trial includes data from the Phase 2 dose-ranging trial, in vitro studies and animal models of infection. The pre-specified NI margin of -15% was considered acceptable to support a limited use claim. This approach is consistent with the guidance on developing antibacterial drugs for the treatment of serious bacterial diseases.¹

The primary analysis population was the microbiological modified intent-to-treat (mMITT) population, which included all patients who received study medication and had at least one baseline uropathogen. The mMITT population excluded patients with organisms resistant to study drugs. The primary efficacy endpoint in the trial was a co-primary endpoint of composite cure (clinical success and microbiologic eradication) at Day 5 and the Test of Cure (TOC) visits. For antibacterial drugs with an intravenous formulation alone, clinical and

¹ Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases <https://www.fda.gov/downloads/Drugs/Guidances/UCM359184.pdf>

microbiological success at the end of IV therapy and TOC visits is recommended as a co-primary endpoint in the current FDA guidance on developing antibacterial drugs for the treatment of cUTI.²

The mMITT population consisted of 388 patients with cUTI, including 162 (41.8%) with pyelonephritis. The median age was 64 years, 52.8% were female and 99.5% were White. The majority of the patients (99%) were enrolled from Eastern Europe. Only three patients were from the United States. Concomitant bacteremia was identified in 25 (13.1%) and 23 (11.7%) patients at baseline in the plazomicin and meropenem arms, respectively. In both treatment arms, the median treatment duration of IV therapy was 6 days.

At Day 5, composite cure rates in the plazomicin arm were 88% (168/191) and 91.4% (180/197) in the meropenem arm, treatment difference of -3.4 (95 % confidence intervals (CI), -10.0, 3.1). At the TOC visit, composite cure rates in the plazomicin arm were 81.7% (156/191) and 70.1% (138/197) in the meropenem arm, treatment difference of 11.6 (95 % CI, 2.7, 20.3). Treatment effects were consistent across subgroups and in sensitivity analysis.

The main shortcoming of the trial was that patients were primarily enrolled from Eastern Europe and only three patients were enrolled in the US. Study 002, however enrolled patients from the US and so provides information that the treatment effect seen in Study 009 is applicable to the US population.

Bloodstream Infections

The Applicant is seeking the BSI indication based on the results of a Phase 3 trial (Study 007) in patients with Hospital-Acquired Bacterial Pneumonia (HABP)/Ventilator-Associated Bacterial Pneumonia (VABP) or BSI due to carbapenem-resistant Enterobacteriaceae (CRE).

(b) (6)
(b) (6)

² Complicated Urinary Tract Infections: Developing Drugs for Treatment, <https://www.fda.gov/downloads/Drugs/Guidances/ucm070981.pdf>

(b) (4)

While the Applicant is seeking approval for BSI under the LPAD pathway, it is important to note that for products approved under this pathway, the standards for approval still must be met and evidence from

adequate and well-controlled trials still need to be provided to support approval. The rules of construction set forth in section 506(h)(8) of the FD&C Act reiterate that the LPAD pathway provision does not alter FDA approval standards under the FD&C Act or the PHS Act, including the standards of evidence and applicable conditions for approval under these Acts.

Safety

From a safety standpoint, the safety signals seen are consistent with that seen with aminoglycosides. The safety database of 590 plazomicin-treated patients includes 377 patients with cUTI who received the proposed 15 mg/kg dose. The common adverse reactions reported by > 1 % of plazomicin-treated patients were decreased renal function, diarrhea, hypertension headache, nausea, vomiting and hypotension. In Study 009, the incidence of adverse reactions associated with renal function (acute kidney injury, serum creatinine increased, chronic kidney disease, creatinine clearance decreased, renal failure, renal impairment) was 3.6% (11/303) in plazomicin-treated patients compared with 1.3% (4/301) in meropenem-treated patients. Serum creatinine increases of 0.5 mg/dL or greater above baseline occurred in 7% (21/300) of plazomicin-treated patients compared with 4% (12/297) of meropenem-treated patients. These increases mainly occurred in patients with CLcr \leq 90 mL/min and were associated with a plazomicin trough level (Cmin) greater than or equal to 3 mcg/mL. In Study 009, there was one case of reversible hypoacusis in a plazomicin-treated patient and one case of tinnitus in a meropenem-treated patient. In Study 002, one case each of irreversible tinnitus and reversible vertigo were reported in plazomicin-treated patients, and one case of an abnormal audiogram occurred in a levofloxacin-treated patient.

Labeling includes safety information that have been associated with the aminoglycoside class of drugs including neuromuscular blockade, fetal harm, and *Clostridium difficile* associated diarrhea.

Therapeutic Drug Monitoring (TDM) was not used in the cUTI trials. Based on the analysis of data in the NDA, it appears that the risk of nephrotoxicity increases with trough concentrations greater than 3 mcg/mL. Hence, labeling will include recommendations for TDM in patients with creatinine clearance \geq 15 mL/min to < 90 mL/min to maintain plazomicin trough concentrations below 3 mcg/mL. For patients with plazomicin trough concentrations greater than 3 mcg/mL, the dosing intervals will need to be extended by 1.5-fold. The in vitro diagnostic device to measure plazomicin concentrations was not considered a companion diagnostic as it was not considered essential for the safe and effective use the drug. (b) (4)

In conclusion, the Applicant has provided substantial evidence to support the safety and efficacy of plazomicin for the treatment of cUTI, including acute pyelonephritis in adults with limited or no treatment options. The safety findings support an acceptable benefit-risk for its use for the treatment of cUTI, including pyelonephritis in patients with limited or no treatment options. The safety findings observed in the cUTI trial and recommendations to monitor plazomicin trough concentrations to mitigate the risk for nephrotoxicity will be described in labeling.

Postmarketing requirements (PMRs) include pediatric studies under PREA (b) (4). The postmarketing commitments include a pharmacokinetic study in patients on hemodialysis who receive plazomicin and a commitment to establish an FDA cleared or approved in-vitro diagnostic device for TDM of plazomicin to be used in the management of patients with cUTI.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p>Analysis of Condition</p>	<p>Complicated urinary tract infections are a clinical syndrome characterized by pyuria, a documented microbial pathogen on culture of urine or blood, accompanied by fever, chills, flank pain, back pain, and/or costo-vertebral angle pain or tenderness, that occur in the patients with a functional or anatomical abnormality of the urinary tract or in the presence of catheterization. Patients with pyelonephritis are considered a subset of patients with cUTI, regardless of underlying abnormalities of the urinary tract.</p> <p>The majority of cUTI are caused by Gram-negative bacteria of the family Enterobacteriaceae. In recent years, bacteria resistant to antibacterial drugs commonly used for the treatment of cUTI are increasing.</p>	<p>Complicated UTI is a serious bacterial infection most commonly caused by Gram-negative bacteria of the family Enterobacteriaceae.</p>
<p>Current Treatment Options</p>	<p>Quinolones and cephalosporins have been the most commonly used antibacterial drugs for the treatment of cUTI. The spread of extended-spectrum-beta-lactamase (ESBL)-producing bacteria and development of resistance to quinolone antibacterial drugs, however, has limited the available treatment options for patients with cUTI.</p>	<p>Although some treatment options are currently available for the treatment of cUTI, new therapies are an important addition to the armamentarium due to emergence of multidrug resistance among some of the causative bacteria.</p>
<p>Benefit</p>	<p>The efficacy of plazomicin in the treatment of cUTI including pyelonephritis was demonstrated in a randomized, double-blind, Phase 3 trial demonstrating noninferiority of plazomicin to meropenem. Subjects could be switched to oral antibacterial drugs such as levofloxacin after at least 5 days of IV therapy.</p> <p>A single Phase 3 trial along with supportive evidence was considered adequate for a limited use cUTI indication. Supportive evidence for the single trial was provided by a dose-ranging Phase 2 trial in patients with cUTI, in vitro</p>	<p>The results of the Phase 3 cUTI trial along with the supportive information provide sufficient evidence to support the efficacy of plazomicin in treatment of cUTI including pyelonephritis in patients with limited or no treatment options.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>studies, and evidence of activity from animal models of infection.</p> <p>The co-primary efficacy endpoint was clinical success and microbiologic eradication at the Day 5 and the TOC visits. This is consistent with the current FDA guidance for developing drugs for treatment of cUTI.</p> <p>Overall success rates at the Day 5 visit were 88.5% in the plazomicin arm and 91.4% in the meropenem arm (treatment difference -3.4%, (95% CI -10.0, 3.1). At the TOC visit, the rates of clinical cure and microbiologic eradication at the TOC visit were 81.7% in the plazomicin arm and 70.1% in the meropenem arm (treatment difference 11.6 (95% CI 2.7, 20.3).</p>	
Risk	<p>In the clinical trials, the safety concerns observed were consistent with that seen with the aminoglycoside class of drugs. The incidence of adverse reactions associated with renal function (acute kidney injury, serum creatinine increased, chronic kidney disease, creatinine clearance decreased, renal failure, renal impairment) was 3.6% (11/303) in plazomicin-treated patients compared with 1.3% (4/301) in meropenem-treated patients. Serum creatinine increases of 0.5 mg/dL or greater above baseline occurred in 7% (21/300) of plazomicin-treated patients compared with 4% (12/297) of meropenem-treated patients. These increases mainly occurred in patients with CLcr ≤ 90 mL/min and were associated with a plazomicin trough level (C_{min}) greater than or equal to 3 mcg/mL.</p>	<p>Plazomicin demonstrated an acceptable risk-benefit profile in the treatment of cUTI in patients with limited or no treatment options.</p>
Risk Management	<p>The Applicant has agreed to establish an FDA cleared or approved in-vitro diagnostic device for TDM of plazomicin for patients with cUTI.</p>	<p>In addition to dosing recommendations based on creatinine clearance, TDM is recommended in labeling to mitigate the risk of nephrotoxicity.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		<p>In addition to the safety information from the cUTI trial, regarding nephrotoxicity and ototoxicity, the prescribing information will include warnings that have been associated with the aminoglycoside class of drugs including neuromuscular blockade, and fetal harm, and antibacterial drug class labeling regarding risk of <i>Clostridium difficile</i> associated diarrhea.</p>

2. Background

Plazomicin is an aminoglycoside antibacterial drug derived from sisomicin. Plazomicin has activity in the presence of some aminoglycoside modifying enzymes (AMEs). As with other aminoglycosides, plazomicin is thought to exert concentration-dependent bactericidal effect through inhibition of protein synthesis.

Plazomicin is active in vitro against many members of the Enterobacteriaceae class, including *Escherichia coli* and *Klebsiella pneumoniae*. Plazomicin has no in vitro activity against streptococci (including *Streptococcus pneumoniae*), enterococci (including *Enterococcus faecalis*, *E. faecium*), anaerobes, *Stenotrophomonas maltophilia* and Acinetobacter spp. and has variable activity against *Pseudomonas aeruginosa*.

Plazomicin was granted Qualified Infectious Disease Product designation for the following indications: hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), complicated intra-abdominal infections (cIAIs), cUTI, and catheter-related BSI, Fast Track designation for the treatment of serious and life-threatening infections due to carbapenem resistant Enterobacteriaceae (CRE) and Breakthrough Therapy designation for the treatment of BSIs caused by certain Enterobacteriaceae in patients who have limited or no alternative treatment options.

In this NDA, the Applicant is seeking approval of plazomicin for the following indications:

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

As only limited clinical safety and efficacy data for plazomicin are currently available, plazomicin should be reserved for use in patients who have limited or no alternative treatment options.

2. For patients aged 18 years or older for the treatment of bloodstream infections (BSIs) caused by the following susceptible microorganism(s): *Klebsiella pneumoniae* and *Escherichia coli*.

As only limited clinical safety and efficacy data for plazomicin are currently available, plazomicin should be reserved for use in patients who have limited or no alternative treatment options.

The Applicant requested review of the BSI indication under section 506(h) of the Federal Food, Drug and Cosmetic Act (FD&C Act). Section 506(h) of the FD&C Act establishes a limited population pathway for antibacterial and antifungal drugs (LPAD pathway). The LPAD pathway provides that FDA may approve an antibacterial or antifungal drug that is

intended to treat serious or life-threatening infections in a limited population of patients with unmet needs.³

As noted in the LPAD pathway draft guidance, Section 506(h) of the FD&C Act provides that FDA may approve an antibacterial or antifungal drug, alone or in combination with one or more other drugs, under the LPAD pathway, if:

- The drug is intended to treat a serious or life-threatening infection in a limited population of patients with unmet needs;
- The standards for approval under section 505(c) and (d) of the FD&C Act (21 U.S.C.355) or the standards for licensure under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262), as applicable, are met; and
- FDA receives a written request from the sponsor to approve the drug as a limited population drug (see section VI.B., Written Request for Approval Under the LPAD Pathway).

For an application under the LPAD pathway, substantial evidence of effectiveness for the drug's intended use is required. The rules of construction set forth in section 506(h)(8) of the FD&C Act reiterate that the LPAD pathway provision does not alter FDA approval standards under the FD&C Act or the PHS Act, including the standards of evidence and applicable conditions for approval under these Acts.

3. Product Quality

The proposed drug substance, plazomicin sulfate (b) (4)
(b) (4) The stability data submitted in the NDA support the proposed drug substance retest date of (b) (4) months when stored (b) (4)
(b) (4)
(b) (4)

The drug product is supplied as a 10-mL sterile, aqueous solution for intravenous infusion, containing 500 mg of plazomicin (b) (4) in a single-dose vial with a rubber stopper and a flip-top cap. The only excipients in the formulation are sodium hydroxide, NF and Water for Injection, USP, which are both compendial. The specifications include tests relevant for the proposed dosage form, such as appearance, identity, degradants, assay, pH, particulates, endotoxins, and sterility.

The container-closure system consists of 10-mL (b) (4) Type I clear glass vial and (b) (4) sealed with 20 mm aluminum flip-off seal with royal blue polypropylene button. The overall information provided in the NDA for the container closure system, including the extractable and leachable data, was found to be acceptable.

³ Limited Population Pathway for Antibacterial and Antifungal Drugs Guidance for Industry
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM610498.pdf>

Stability data for four batches manufactured by (b) (4) and three batches manufactured by (b) (4) have been provided in the NDA. This includes 24 months of long-term data at 5°C for three registration stability batches, manufactured at (b) (4). The proposed expiration dating period of 36 months was found to be acceptable.

The overall information regarding the manufacturing process provided in the NDA and subsequent amendments was found acceptable. The overall product quality microbiology information provided in the NDA was found acceptable.

(b) (4) is responsible for drug substance manufacturing, packaging, release testing and stability testing, and (b) (4) is responsible for drug product manufacturing, packaging, labeling, release and stability testing. In addition, several other sites are involved in the drug substance testing, and the drug product testing, labeling and secondary packaging. The (b) (4) site has been found acceptable for the proposed manufacturing operations. The Applicant has also proposed (b) (4) for commercial drug product. This was found to be acceptable.

The manufacturing and testing facilities for this NDA are deemed acceptable. The OPQ review team recommends approval of the NDA. We agree that there are no product quality issues that preclude approval of this NDA.

4. Nonclinical Pharmacology/Toxicology

Dr. Amy Ellis, PhD, is the pharmacology-toxicology reviewer for this NDA.

Dr. Ellis notes that the nonclinical toxicity profile of plazomicin is similar to that of other aminoglycosides. The kidney was the primary target organ of toxicity in rats and dogs. Clinical signs suggestive of neural blockade were observed in rats following high doses of plazomicin. Plazomicin was not mutagenic (Ames assay) or clastogenic (human lymphocytes in vitro or rat bone marrow in vivo).

In a fertility and early embryonic development study, male and female rats received subcutaneous plazomicin at 0, 8, 25, or 50 mg/kg/day from prior to pairing through the mating and postmating period. Parental toxicity (reduced food consumption and body weight gain) was observed at the mid and high doses. Plazomicin had no adverse effects on fertility in male rats at up to 50 mg/kg/day, resulting in an exposure (AUC) approximately 0.8-fold the human AUC at dose of 15 mg/kg once daily. In female rats, dosed at 25 and 50 mg/kg/day, fewer corpora lutea, leading to fewer uterine implantation sites and viable embryos per dam were seen. The no observed effect level (NOEL) for fertility and reproductive performance in female rats was 8 mg/kg/day (0.1-fold human AUC). No adverse effects were seen on pregnancy or peri/postnatal development of offspring when plazomicin was given to rat dams during fetal organogenesis and through lactation.

Dr. Ellis recommends approval of the NDA from a nonclinical pharmacology-toxicology perspective. We agree that there are no nonclinical issues that preclude approval of this NDA.

5. Clinical Pharmacology

Kunyi Wu, PharmD and Luning (Ada) Zhuang PhD are the clinical pharmacology reviewers for this NDA. This review will focus primarily on clinical pharmacology aspects of the NDA that are pertinent to the cUTI indication.

Following a single intravenous (IV) dose of plazomicin, both C_{max} and AUC_{0-24} increased in an approximately dose-proportional manner from 1 mg/kg to 15 mg/kg. Plazomicin does not appear to be metabolized to any appreciable extent. Plazomicin is primarily excreted by the kidneys. Following a single IV dose of 15 mg/kg radiolabeled plazomicin, approximately 97.5% of the dose was recovered in the urine as unchanged plazomicin. The geometric mean (% CV) total body clearance of plazomicin and renal clearance in healthy adults following a single IV dose of plazomicin 15 mg/kg were 4.76 L/h (17.1%) and 4.64 (23.5%), respectively. The mean half-life of plazomicin in healthy adults is 3.53 hours.

The mean percentage protein binding of plazomicin in human plasma was 19.6% (range, 13.9% to 24%). The protein binding was not concentration dependent in the range from 5 µg/mL to 100 µg/mL.

The C_{max} , C_{min} , and AUC_{0-24} following repeated daily administration increased in an approximately dose-proportional manner from 4 mg/kg QD to 15 mg/kg QD. There was no appreciable accumulation at steady-state for once daily dosing in subjects with normal renal function. The half-life of plazomicin increased by approximately 2-fold and 4-fold in subjects with moderate and severe renal impairment, respectively, compared to subjects with normal renal function.

Plazomicin is not a substrate of P-gp or BCRP transporters at a concentration up to 17.8 µg/mL which is equivalent to 22.3 µg/mL in vivo with 20% protein binding. Plazomicin is not an inhibitor of P-gp, BCRP, MRP2, OATP1B1, OATP1B3, OAT1, OAT3, OCT1 or OCT2. It is an inhibitor of MATE1 and MATE2-K transporters in vitro. Plazomicin does not inhibit or induce the common CYP enzymes.

The Applicant did not conduct exposure-response (E-R) analysis for efficacy in cUTI patients. The clinical pharmacology team performed an analysis in cUTI patients to assess the relationship between total plazomicin AUC_{0-24} :MIC ratio after the first dose in Study 009 using the composite microbiology and clinical response at Day 5 and TOC and microbiology response at Day 5 and at TOC. A flat E-R relationship was identified between AUC_{0-24} :MIC ratio and the four efficacy endpoints.

Renal function is one of the key intrinsic factors that affects dosing and dose adjustment is needed in patients with creatinine clearance (CL_{cr}) less than 60 mL/min. Six subjects with severe renal impairment (CL_{cr} from 15 to 29 mL/min) were enrolled in a PK study in subjects with renal impairment and one patient in Study 009. E-R analysis for nephrotoxicity (defined as an increase of serum creatinine concentration ≥ 0.5 mg/dL from baseline), identified a higher risk of nephrotoxicity in patients with mild or moderate renal impairment (CL_{cr} > 30-90 mL/min) compared to patients with CL_{cr} >90 mL/min. As plazomicin may be a therapeutic

option for some patients with severe renal impairment, the proposed initial dose for patients with CLCr >15 to 30 mL/min was evaluated based on simulated exposures of plazomicin across different renal function groups. The exposure (AUC_{0-48h}) in patients with CLCr >15 to 30 mL/min receiving plazomicin 10 mg/kg q48h was simulated based on the population PK model and compared with that in patients with CLCr >30 mL/min. This analysis showed that AUC_{0-48h} in patients with CLCr >15 to 30 mL/min receiving 10 mg/kg q48h would be similar to that seen in patients in other renal function groups. Therefore, the clinical pharmacology review team provided dosing recommendations for plazomicin in patients with severe renal impairment (Table 1).

The Applicant proposed C_{min}-based TDM in cUTI patients with CLCr > 15 to 60 mL/min or in those for whom more than 5 days of plazomicin therapy is anticipated to mitigate the risk of nephrotoxicity. The Applicant also proposed (b) (4)

Based on the review team’s E-R analysis for nephrotoxicity in cUTI patients, an increase in serum creatinine concentration of ≥ 0.5 mg/dL, was independent of the duration of treatment with plazomicin. In addition, in the cUTI trials, the incidence of nephrotoxicity was higher in patients with CLCr < 90 mL/min compared to those with CLCr > 90 mL/min. The clinical pharmacology review team recommends C_{min}-based TDM in patients with CLCr < 90 mL/min. The results of a classification and regression tree (CART) analysis in cUTI patients indicated that a C_{min} of 3 mcg/mL is a critical cut-off associated with a higher incidence of nephrotoxicity.

The agreed to dosing recommendations for plazomicin are provided in Table 1.

Table 1: Dosing Recommendations

Estimated CLCr ^a (mL/min)	Recommended Dosage ^b	Dosing Interval (b) (4)
≥ 60 - < 90	15 mg/kg	Every 24 hours
≥ 30 - < 60	10 mg/kg	Every 24 hours
≥ 15 - < 30	10 mg/kg	Every 48 hours

^a CLCr estimated by the Cockcroft-Gault formula

^b Using Total Body Weight (TBW); for patients with TBW greater than IBW by (b) (4) % adjusted body weight

As the PK study in patients with renal impairment did not include any subjects on hemodialysis, the clinical pharmacology review team recommends a postmarketing commitment to evaluate the PK of plazomicin in patients on hemodialysis. The Applicant has agreed to conduct this study.

Drs. Wu and Zhuang recommend approval of the NDA from a clinical pharmacology perspective. We agree that there are no clinical pharmacology issues that preclude approval of the NDA.

6. Clinical Microbiology

Simone Shurland, PhD is the clinical microbiology reviewer for this NDA.

In surveillance studies, plazomicin MIC₉₀ values ranged from 0.5 mcg/mL - ≤ 2 mcg/mL against *E. coli*, *Klebsiella spp.*, *Citrobacter spp.*, *Enterobacter spp.*, and *Serratia marcescens*. Plazomicin MIC₉₀ values ranged from 2-8 mcg/mL against *Proteus mirabilis* and indole-positive *Proteus spp.*, *Providencia spp.* and *Morganella spp.* Plazomicin has no in vitro activity against streptococci (including *S. pneumoniae*), enterococci (including *E. faecalis*, *E. faecium*), anaerobes, *S. maltophilia* and *Acinetobacter spp.* and has variable activity against *P. aeruginosa*.

Resistance to aminoglycosides is mediated by multiple mechanisms including impaired membrane permeability, efflux mechanisms, ribosomal alterations or expression of aminoglycoside modifying enzymes (AMEs). Bacterial isolates that produce 16S rRNA methyltransferases (RMT) have plazomicin MICs of ≥ 128 mcg/mL. Overexpression of efflux pumps (e.g., *acrAB-tolC*) or reduced expressions of porins (e.g., *ompF* or *ompK36*) results in elevations in plazomicin MICs. The spontaneous mutation frequency for plazomicin against Enterobacteriaceae with different AMEs and β-lactamases (*E. coli* and *K. pneumoniae*) ranged from 3.0 x 10⁻¹⁰ to 4.21 x 10⁻⁷ when plazomicin was tested at 4x – 8x MIC.

Plazomicin is not inhibited by most AMEs known to affect gentamicin, tobramycin, or amikacin, including acetyltransferases (AACs), phosphotransferases (APHs) and nucleotidyltransferases (ANTs). No data are available on its activity against organisms that are resistant to all available aminoglycosides. Activity of plazomicin was demonstrated in vitro against Enterobacteriaceae in the presence of certain beta-lactamases, including extended-spectrum beta-lactamases (TEM, SHV, CTX-M, AmpC), serine carbapenemases (KPC-2, KPC-3), and oxacillinase (OXA-48). Bacteria producing metallo-beta-lactamases often co-express 16S rRNA methyltransferase, conferring resistance to plazomicin.

Activity of plazomicin was demonstrated in immunocompetent and neutropenic animal models of infections including septicemia, UTI, lung and thigh infection with either amikacin-non-susceptible, gentamicin-non-susceptible, or beta-lactamase producing Enterobacteriaceae.

In Study 009, development of resistance to plazomicin (defined as ≥4-fold increase in plazomicin MIC compared to baseline MIC) occurred in 7 isolates from 6 plazomicin-treated patients. Five of the 7 isolates with decreased plazomicin susceptibility were obtained on or before the end of IV (EOIV) visit, the remaining two were detected at the TOC and LFU visits. Five isolates had plazomicin MICs > 128 mcg/mL in which RMTs were detected, the remaining 2 isolates had 8-64 fold change in MIC (no RMTs were detected in these isolates).

(b) (4)

The following susceptibility test interpretive criteria were agreed to with the Applicant and will be available at www.fda.gov/stic.

Table 2: Susceptibility Test Interpretive Criteria

Pathogen	Minimum Inhibitory Concentration (mcg/mL)			Disk Diffusion Zone Diameter (mm)		
	S	I	R	S	I	R
Enterobacteriaceae	≤2	4	≥8	≥16	14-15	≤13

For a detailed rationale for the STIC, please refer to an addendum from the clinical pharmacology, microbiology, and clinical review teams.

In summary, the probability of target attainment analysis (PTA) using the PK/PD target of 1- \log_{10} CFU reduction support a susceptible breakpoint of 1 mcg/mL. Considerable variability in the PK/PD target was found across the different models (neutropenic mouse thigh and lung and chemostat). The most conservative target was seen in the neutropenic murine thigh infection model (AUC/MIC of 89 for 1- \log_{10} CFU reduction). In general, as cUTI is a serious infection, we have used a PK/PD target of 1- \log_{10} CFU reduction in a neutropenic murine thigh infection model to evaluate the PTA. Only 62-73% of simulated cUTI patients with varying renal function achieve the PK/PD target for 1- \log_{10} CFU reduction at MIC = 2 mcg/mL compared to >90% at MIC=1 mcg/mL. With the proposed dose, >90% of simulated cUTI patients achieved the PK/PD target for net stasis of CFU from baseline (i.e., 24 of AUC/MIC) at MIC = 2 mcg/mL. In the clinical trials, there were only a few patients with cUTI who had a baseline organism with MICs of 2 or 4 mcg/mL. The majority of baseline isolates had MICs of 1 mcg/mL or less. The clinical and microbiologic outcomes in patients with MIC of 2 mcg/mL were 75% (9/12) and 91.7% (11/12) in the plazomicin and meropenem arms, respectively. There were 6 isolates from 6 different patients that had MICs of 4 mcg/mL, all isolates were eradicated at Day 5 and TOC visit and all 6 patients were clinical cures. There are no clinical data in patients with concurrent bacteremia from the cUTI trial where the baseline isolate had MICs greater than 1 mcg/mL. The MICs for the baseline organisms in patients with concurrent bacteremia was 0.5 mcg/mL or less.

cUTI is a serious infection that could be associated with bacteremia and mortality and it is possible that plazomicin will likely be used in more seriously and potentially critically ill patients in clinical settings as compared to those enrolled in the cUTI trial. Clinical outcomes in the subgroup of patients with bacteremia in the plazomicin arm was similar to that seen in the meropenem arm. Given these considerations, the Applicant's proposal of a susceptible breakpoint of (b) (4) mcg/mL was not acceptable (b) (4) and the PK/PD target for 1- \log_{10} CFU reduction was attained in only (b) (4). A breakpoint of 2 mcg/mL can be supported based on the clinical and microbiologic outcomes of 12 patients and the overall distribution of isolates (with the wild type distribution ending at an MIC of 4 mcg/mL). The intermediate breakpoint of 4 mcg/mL also provides for a buffer for a 2-fold margin of error with MIC testing.

Dr. Shurland recommends approval of the NDA from a clinical microbiology perspective. We agree that there are no clinical microbiology issues that preclude approval of the NDA.

7. Clinical/Statistical-Efficacy

Complicated Urinary Tract Infections (cUTI):

Hengrui Sun, DrPH was the statistics reviewer and Shrimant Mishra, MD MPH was the clinical reviewer for this indication.

The Applicant has conducted two trials in support of the cUTI indication, a phase 2 dose-ranging trial and a Phase 3 noninferiority (NI) trial.

Study ACHN-490-002 (Study 002) was a Phase 2 trial, in which two plazomicin doses, 10 mg/kg and 15 mg/kg were evaluated; levofloxacin was the comparator. Plazomicin was administered for 5 days and no oral switch to other antibacterial drugs was allowed. Patients with creatinine clearance < 60 mL/min were excluded. The primary endpoint was microbiologic eradication at the TOC visit. In the MITT population, microbiologic eradication rates were 50% (6/12) in the 10 mg/kg arm, 60.8% (31/51) in the 15 mg/kg arm, and 58.6% (17/29) in the levofloxacin arm.

Study ACHN-490-009 (Study 009) was a Phase 3, randomized, double-blind, NI trial, in which patients \geq 18 years of age with cUTI, including acute pyelonephritis, were randomized to IV plazomicin (15 mg/kg/day) or IV meropenem (1.0 g every 8 hours). The dose of plazomicin was adjusted based on renal function. After a minimum of 4 days of IV therapy, patients could be switched to open-label oral levofloxacin for an additional 3 to 6 days to complete therapy. The maximum duration of IV therapy was 7 days.

Clinical response and microbiological response were assessed at Day 5, End of IV (EOIV, within 24 hours of last dose of IV study drug), TOC (Day 17 ± 2 days), and Late Follow up (LFU, Day 24 – 32). The co- primary endpoints were a composite of microbiologic eradication and clinical cure rate in the microbiologic modified intent-to-treat (mMITT) population at the Day 5 and TOC visits. The mMITT population was defined as all randomized patients who received any dose of study drug and had at least one baseline pathogen which was susceptible to meropenem and plazomicin. The pre-specified NI margin was -15%.

A total of 609 patients were randomized; the mMITT population included 388 patients, 191 in the plazomicin arm and 197 in the meropenem arm. Demographics and baseline characteristics were generally balanced between the two arms. The majority of patients were from Eastern European countries, were predominantly white, mean age was 59.4 years, and 47% were males; approximately 40% had acute pyelonephritis. Only three patients were enrolled from the US. The most common baseline uropathogen identified was *E. coli* (~70%). About 80% of patients were switched to oral therapy after at least 4 days of IV therapy. The median treatment duration of IV study drug was 6 days in both groups.

In the mMITT population, 52 baseline Enterobacteriaceae isolates in 51/189 (27%) patients in the plazomicin arm were non-susceptible (defined as intermediate or resistant) to gentamicin, or tobramycin or both. Only one of these isolates had intermediate susceptibility to amikacin and this isolate was also resistant to gentamicin and tobramycin. Concomitant bacteremia was

identified in 25 (13.1%) and 23 (11.7%) patients in the mMITT population at baseline in the plazomicin and meropenem arms, respectively.

Plazomicin was noninferior to meropenem for the treatment of cUTI for the co-primary endpoints assessed at the Day 5 and TOC visits. The lower bound of the 95% confidence intervals (CI) for the composite endpoint of clinical response and microbiologic eradication were within the pre-specified NI margin of -15% at both visits. Results were generally consistent for the individual components of the composite endpoints (Table 3). Results were also consistent across the various subgroups analyzed.

Table 3: Outcomes in the mMITT Population at Day 5 and TOC Visits

Analysis Visit	Plazomicin n/N (%)	Meropenem n/N (%)	Treatment Difference (95% CI)
Day 5	168/191 (88.0)	180/197 (91.4)	-3.4 (-10.0, 3.1)
Clinical Response*	171/191 (89.5)	182/197 (92.4)	
Microbiological Eradication	188/191 (98.4)	193/197 (98.0)	
TOC	156/191 (81.7)	138/197 (70.1)	11.6 (2.7, 20.3)
Clinical Response^	170/191 (89.0)	178/197 (90.4)	
Microbiological Eradication	171/191 (89.5)	147/197 (74.6)	

*Cure/improvement; ^ Cure; Treatment difference (plazomicin-meropenem)

Drs. Sun and Mishra note that adequate information has been provided in the NDA to support the efficacy and safety of plazomicin for the treatment of cUTI in adults who have limited or no alternative treatment options. In an adequate and well-controlled trial, plazomicin was noninferior to meropenem for the primary composite endpoint (clinical cure and microbiologic eradication) at the Day 5 and TOC visits. The findings were also consistent across subgroups and in sensitivity analyses. Data from a single trial are supported by findings from the Phase 2 trial. Both also note that Study 009 primarily enrolled patients from Eastern Europe and so does not reflect the diversity seen in the US population. Study 002, however enrolled patients from the US and so provide information supporting that the treatment effect seen in Study 009 is applicable to the US population.

Drs. Sun and Mishra recommend approval of the NDA for the cUTI indication. We agree with their assessment.

Bloodstream Infections

Study ACHN007 (Study 007) was a Phase 3, multicenter, randomized, open-label trial in which the efficacy and safety of plazomicin was compared to colistin in patients with HABP/VABP or BSI due to CRE. (b) (4)

(b) (4)

While the Applicant is seeking approval for BSI under the LPAD pathway, it is important to note that for products approved under this pathway, the standards for approval still must be met and evidence from adequate and well-controlled trials still need to be provided to support approval. The rules of construction set forth in section 506(h)(8) of the FD&C Act reiterate that the LPAD pathway provision does not alter FDA approval standards under the FD&C Act or the PHS Act, including the standards of evidence and applicable conditions for approval under these Acts.

8. Safety

The overall safety database included six phase 1 studies, one phase 2 study in cUTI, one phase 3 study cUTI and one study in BSI/HABP/VABP. Across all studies, 612 subjects received at least one dose of plazomicin. This review will focus primarily on the safety findings from the cUTI trials.

In the safety population of the cUTI trials, the median duration of plazomicin therapy was 5 days.; 12% received < 4 days of therapy and no subject received > 7 days of therapy.

There was one death in the plazomicin arm in a 63- year old woman admitted for pyelonephritis. No deaths were reported in the meropenem arm. This patient was discontinued from study drug due to acute kidney injury after having received one dose of plazomicin and switched to piperacillin-tazobactam. At the time of study drug discontinuation, she was found to have metastatic uterine cancer with possible involvement of the lungs and liver. She continued to have worsening renal function (Day 7 creatinine 8.6 mg/dL) and eventually needed hemodialysis. She underwent six sessions of hemodialysis but on Day 17 refused further sessions due to difficulties in tolerating the procedure and died on Day 18. Although

the cause of death is unlikely to be due to study drug, the acute kidney injury may have been related to study drug.

In Study 009, five subjects in each treatment arm had SAEs. In the plazomicin arm, the SAEs were acute kidney injury and metastatic neoplasm in one subject, acute kidney injury, pneumonia, urosepsis, and urinary calculus. Dr. Mishra reviewed the narratives of the five plazomicin-treated patients and notes that the SAE was probably related to the plazomicin in the two acute kidney injury cases. In both cases, decreases in creatinine clearance were noted after only one dose of plazomicin. One subject eventually required hemodialysis and died as noted above, while the second had recovery of renal function.

In Study 009, six subjects in each arm discontinued study drug. In the plazomicin arm, all discontinuations were related to renal injury/function. The protocol required discontinuation of IV study drug in patients with two successive creatinine clearance measurements <30 mL/min during IV treatment. Of the 6 discontinuations in the plazomicin arm, four had baseline creatinine clearance between 30-40 mL/min. In Study 002, 4 plazomicin-treated patients had discontinuations due to adverse events of dizziness (2 subjects), vertigo, diabetes mellitus, azotemia, and hypotension (each reported by 1 patient).

The most common adverse reactions reported by $\geq 1\%$ of plazomicin-treated patients were decreased renal function (this included several similar adverse reactions describing nephrotoxicity), diarrhea, hypertension, headache, nausea, vomiting and hypotension.

Nephrotoxicity

In Study 009, serum creatinine increases of ≥ 0.5 mg/dL occurred in 7.0% (21/300) of plazomicin-treated patients compared with 4.0% (12/297) of meropenem-treated patients; 3.7% (11/300) and 3% (9/297) occurred during IV therapy in plazomicin and meropenem-treated patients, respectively. By the last follow-up visit (between 8 to 43 days after completion of IV therapy), in 9/11 plazomicin-treated patients and all meropenem-treated patients renal function had recovered. Serum creatinine increases of ≥ 0.5 mg/dL above baseline were also observed following completion of IV therapy.

In cUTI patients with CLcr of $> 30-90$ mL/min, 9.7% (20/207) plazomicin-treated and 4.1% (9/217) of meropenem-treated patients had serum creatinine increases of ≥ 0.5 mg/dL above baseline. In cUTI patients with CLcr > 90 mL/min, 1.1% (1/93) of plazomicin-treated and 3.8% (3/80) meropenem-treated patients had serum creatinine increases of ≥ 0.5 mg/dL.

In Study 009, adverse reactions related to renal function such as acute kidney injury, serum creatinine increased, chronic kidney disease, creatinine clearance decreased, renal failure, renal impairment was reported in 3.6% (11/303) of plazomicin-treated patients compared with 1.3% (4/301) meropenem-treated patients.

Table 11: Subjects with Post-Baseline Increases in Serum Creatinine ≥ 0.5 mg/dL (Studies 002 and 009, Safety Population)

Serum Creatinine Increase mg/dL	Study 002		Study 009	
	Plazomicin N=74, N1=72 n/N1 (%)	Levofloxacin N=44, N1=41 n/N1 (%)	Plazomicin N=303; N1=300 n/N1 (%)	Meropenem N=301; N1=297 n/N1 (%)
≥ 0.5	4 (5.6%)	1 (2.4%)	21 (7.0%)	12 (4.0%)
≥ 1.0	0	0	3 (1.0%)	5 (1.3%)
≥ 2.0	0	0	2 (0.7%)	0
≥ 3.5	0	0	1 (0.3%)	0
≥ 4.0	0	0	1 (0.3%)	0

N1= number of patients with a baseline and postbaseline serum creatinine from the central laboratory

Source: Adapted from Table 28 of Sponsor's Summary of Clinical safety

Labeling includes a warning regarding the risk of nephrotoxicity with plazomicin and the data are further described in the Adverse Reactions section of the package insert. In addition to dosing based on creatinine clearance, recommendations are provided in labeling to assess CLcr in all patients prior to initiating therapy and daily during treatment with plazomicin, particularly in those at increased risk of nephrotoxicity, such as those with renal impairment, the elderly, and those receiving concomitant potentially nephrotoxic medications. TDM is recommended for patients with CLcr ≥ 15 mL/min and < 90 mL/min with a recommended trough level of 3 mcg/mL.

Ototoxicity

There were three reports of adverse events (hypoacusis, tinnitus, vertigo) associated with cochlear or vestibular function. The hypoacusis and vertigo events resolved and the tinnitus event was unilateral. In phase 1 studies, 5 plazomicin subjects reported tinnitus but the events were transient and occurred after a single dose. Also in the phase 1 studies, one subject reported transient nystagmus (this subject also had tinnitus), and another subject was reported to have an abnormal vestibular function test.

Pure tone audiometry was performed in the phase 1 and phase 2 studies. Treatment associated ototoxicity could not be definitively excluded per the American Speech-Language-Hearing Association criteria in 2.2% (4/182) of plazomicin-exposed and 2.0% (1/49) of comparator or placebo-exposed adults, based on the assessment of a panel of outside experts used by the Applicant.

Also in the phase 1 studies, a mix of electronystagmography, modified Romberg testing, and Dynamic Visual Acuity testing was performed; modified Romberg testing was also performed in the phase 2 study. The electronystagmography data was also reviewed by independent experts and although abnormal caloric findings were noted in 4/31 subjects whose data were reviewed, they were not associated with AEs suggestive of vestibular toxicity.

A warning regarding risk of ototoxicity has been included in labeling that describes the adverse reactions noted in the clinical trials and includes information regarding aminoglycoside-associated ototoxicity.

9. Advisory Committee Meeting

This NDA was discussed at the Antimicrobials Drug Advisory Committee meeting on May 03, 2018. The committee was asked to vote on two questions.

Question 1: Has the applicant provided substantial evidence of the safety and effectiveness of plazomicin for the treatment of complicated urinary tract infections in patients with limited or no treatment options?

- a. If yes, please provide any recommendations regarding labeling.
- b. If no, what additional studies/analyses are needed?

Voting was as follows:

Yes: 15 No: 0 Abstain: 0

Committee Discussion: The committee unanimously agreed that the applicant provided substantial evidence of the safety and effectiveness of plazomicin for the treatment of complicated urinary tract infections in patients with limited or no treatment options. One committee member was not present to vote.

The committee members noted that plazomicin will be a valuable addition, given the continued emergence of resistance to currently available therapies. The panel also commented on the limited safety database and suggested additional exploration on dosing and markers for nephrotoxicity. The committee also recommended consideration of additional postmarketing safety studies and labeling to include guidance on therapeutic drug monitoring. The committee members also expressed concern regarding the potential for ototoxicity.

Question 2: Has the applicant provided substantial evidence of the safety and effectiveness of plazomicin for the treatment of bloodstream infections in patients with limited or no treatment options?

- a. If yes, please provide any recommendations regarding labeling.
- b. If no, what additional studies/analyses are needed?

Yes: 4 No:11 Abstain: 0 No-Voting: 1

Committee Discussion: The majority of the committee voted that the applicant has not provided substantial evidence of the safety and effectiveness of plazomicin for the treatment of bloodstream infections in patients with limited or no treatment options. One committee member was not present to vote.

(b) (4)



10. Pediatrics

The Applicant requested deferral of pediatric studies because the adult trial of cUTI was completed and the product is ready for approval. [REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

The pediatric plan was discussed at the Pediatric Review Committee (PeRC) on April 18, 2018 and found to be acceptable. The proposed pediatric studies will be postmarketing requirements (PMRs). Very late in the review cycle, after the discussion with PeRC had taken place, the Applicant informed the Agency, that they will be revising their pediatric development program. This will be addressed post-approval.

11. Other Relevant Regulatory Issues

Office of Scientific Investigations Audits

John Lee, MD from the Office of Scientific Investigations (OSI) provided a clinical inspection summary for this NDA. Inspections were conducted for four clinical investigator sites (3 for Study 009 and 1 for Study 007) and the Applicant. A Form FDA 483 was issued at one site in Study 009 for minor GCP deficiencies unlikely to be significant to the study outcome. For all remaining sites, no significant deficiencies were observed and a Form FDA 483 was not issued. The data from the inspected sites appear reliable as reported in the NDA. The study conduct was found to be adequate, including the Applicant's oversight of study conduct. Dr. Lee notes that all audited data were adequately verifiable and appear reliable as reported in the NDA.

Assay for TDM

In the NDA, the Applicant notes that an immunoassay (ThermoFisher) is under development to measure plazomicin concentrations. There have been many discussions between the Applicant, the device manufacturer and the Center for Devices and Radiologic Health (CDRH) regarding this device and the submission to CDRH is pending. [REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED] In Study 009, dosing adjustment was based on creatinine clearance only and TDM was not performed.

Based on the analysis of data in the NDA, it appears that the risk of nephrotoxicity increases with trough concentrations greater than 3 mcg/mL. (b) (4)

An in vitro diagnostic device to measure plazomicin concentrations was not considered a companion diagnostic for cUTI as it was not considered essential for the safe and effective use of the drug for treatment of cUTI.⁶

As TDM was not used in the cUTI trials and availability of an in vitro diagnostic device can further mitigate the risk of nephrotoxicity, labeling will include recommendations for TDM in patients with creatinine clearance ≥ 15 mL/min to < 90 mL/min to maintain plazomicin trough concentrations below 3 mcg/mL. For patients with plazomicin trough concentrations greater than 3 mcg/mL, the dosing intervals will need to be extended by 1.5-fold.

12. Labeling

Labeling recommendations provided by the review team, including OPDP and DMEPA have been incorporated in labeling. The trade name ZEMDRI was considered acceptable by DMEPA. Only the results of the cUTI trials are included in the Adverse Reactions and Clinical Studies section of the label. Labeling also includes information in the Warnings and Precautions section regarding aminoglycoside-associated adverse reactions including nephrotoxicity, ototoxicity, neuromuscular blockade, fetal harm, hypersensitivity reactions and risk for development of *Clostridium difficile*-associated diarrhea.

13. Postmarketing

Following are the postmarketing requirements under PREA:

1. Conduct an open-label multiple dose pharmacokinetic and safety study of plazomicin in hospitalized children ages birth to 18 years with infections and receiving standard-of-care antibacterial drugs.
2. Conduct a randomized active-controlled pharmacokinetic and safety trial of plazomicin in children ages birth to 18 years with cUTI including acute pyelonephritis.

⁶ Guidance on in vitro companion diagnostic devices
<https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf>

Following is a postmarketing requirement under Section 505(o):

1. Conduct US surveillance studies for five years from the date of marketing plazomicin to determine if resistance to plazomicin has developed in those organisms specific to the indication in the label.

The Applicant has agreed to the following postmarketing commitments:

1. Conduct a clinical study in subjects with end stage renal disease (ESRD) receiving hemodialysis to evaluate the pharmacokinetics of plazomicin.
2. Establish an FDA cleared or approved in-vitro diagnostic device for therapeutic drug monitoring of plazomicin that is recommended for patients with baseline creatinine clearance < 90 mL/min for the treatment of cUTI.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUMATHI NAMBIAR
06/25/2018

EDWARD M COX
06/25/2018