

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**210303Orig1s000**

**PRODUCT QUALITY REVIEW(S)**

## OPQ Memorandum for NDA 210303

**Drug Name/Dosage Form:** Zemdri™ (plazomicin) injection

**Strength:** 500 mg/10 mL (per vial)

**Route of Administration:** intravenous

**Applicant:** Achaogen, Inc.

**Recommendation:** Approval

The IQA dated 5/21/2018 had recommended Approval of the NDA but at that time the final assessment of the [REDACTED] (b) (4) was pending. This memorandum captures the assessment of [REDACTED] (b) (4) by OPF and provides a final recommendation from product quality perspective.

OPF notes (Addendum dated 6/15/2018) that based on the API inspection of [REDACTED] (b) (4) and assessment of the subsequent information requests, there are no concerns in the use of the [REDACTED] (b) (4). A post-approval inspection of the drug product facility is recommended.

Since the IQA was finalized, the only outstanding non-approvability issue related to the [REDACTED] (b) (4) has now been successfully resolved.

This NDA is recommended for final **Approval** from product quality perspective.

Bala Shanmugam, PhD.  
Branch Chief, ONDP/OPQ



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Shanmugam

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**Recommendation: *Approval***

**NDA 210303**

**Review # 1**

Drug Name/Dosage Form	Zemdri™ (plazomicin) Injection
Strength	500 mg/10 mL (per vial)
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Achaogen, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	October 25, 2017	All
Amendment (eCTD 005)	January 11, 2018	Drug Product, Drug Substance, Microbiology
Amendment (eCTD 008)	January 19, 2018	<i>Correction to amendment eCTD 005</i>
Amendment (eCTD 018)	February 15, 2018	Drug Substance, Drug Product
Amendment (eCTD 019)	February 20, 2018	Drug Substance, Drug Product
Amendment (eCTD 022)	February 23, 2018	Process, Microbiology
Amendment (eCTD 023)	February 23, 2018	Process, Microbiology
Amendment (eCTD 024)	February 26, 2018	Environmental Assessment
Amendment (eCTD 026)	March 9, 2018	Microbiology
Amendment (eCTD 031)	March 23, 2018	Microbiology
Amendment (eCTD 034)	April 10, 2018	Drug Product, Facilities
Amendment (eCTD 038)	April 12, 2018	Drug Product
Amendment (eCTD 045)	April 26, 2018	Microbiology
Amendment (eCTD 047)	April 30, 2018	Facilities
Amendment (eCTD 049)	May 2, 2018	Drug Product
Amendment (eCTD 050)	May 4, 2018	Drug Product

**Quality Review Team**

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Sithamalli Chandramouli	Charles Jewell
Drug Product	George Lunn	Balajee Shanmugam
Process	Steven Frisbee	Upinder Atwal
Microbiology	Laura Wasil	Stephen Langille
Facilities	Christina Capacci-Daniel	Derek Smith
Biopharmaceutics	Banu Zolnik	Elsbeth Chikhale
Environmental Assessment*	James Laurenson	N/A
Regulatory Business Process Manager	Anh-Thy Ly	N/A
Application Technical Lead	Dorota Matecka	N/A

\* *Environmental Assessment is captured in the Drug Product Chapter*

## Quality Review Data Sheet

### 1. RELATED/SUPPORTING DOCUMENTS

#### A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Review Completed	Comments
(b) (4)	Type III	(b) (4)	(b) (4)	N/A*		
	Type III			N/A*		
	Type III			N/A*		

\*Sufficient information regarding the container/closure system was provided in the NDA

#### B. Other Documents: IND, RLD, or sister applications

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	102563	

### 2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	Complete	Acceptable ( <i>refer to DS and DP reviews</i> )		
CDRH	N/A			
Clinical	N/A			
Other	N/A			

## Executive Summary

### I. Recommendations and Conclusion on Approvability

The NDA, as amended, has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product, plazomicin injection. All information requests and review issues have been addressed and there are no pending approvability issues. The manufacturing and testing facilities for this NDA are deemed acceptable as documented in the Facility Chapter (dated May 17, 2018). The overall manufacturing inspection recommendation in Panorama is still pending (b) (4) however, this inspection recommendation does not impact the NDA recommendation. Based on the above assessments, this NDA is currently recommended for *Approval* by the Office of Pharmaceutical Quality (OPQ).

### II. Summary of Quality Assessments

#### A. Product Overview

ZEMDRI™ Injection contains plazomicin (as plazomicin sulfate), which is a semi-synthetic aminoglycoside antibacterial derived from sisomicin, that acts by binding to bacterial 30S ribosomal subunit inhibiting protein synthesis. Plazomicin was granted Qualified Infectious Disease Product (QIDP) status for the following indications: treatment of hospital acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, complicated intraabdominal infections, and catheter-related bloodstream infections. Plazomicin was also granted Breakthrough Therapy (BT) designation for the treatment of bloodstream infections caused by the following susceptible microorganism(s): *Klebsiella pneumoniae* and *Enterobacter aerogenes* in patients who have limited or no alternative treatment options.

The proposed drug product, Zemdri™ (plazomicin) Injection, 500 mg/10 mL, is supplied as a sterile solution in a glass vial that needs to be further diluted to achieve a final volume of 50 mL for intravenous infusion.

<p><b>Proposed Indication(s) including Intended Patient Population</b></p>	<p>ZEMDRI is indicated in patients 18 years or older for the treatment of complicated urinary tract infections (cUTI) including pyelonephritis caused by the following susceptible microorganism(s): <i>Escherichia coli</i>, <i>Klebsiella pneumoniae</i>, (b) (4) <i>P. mirabilis</i> (b) (4) and <i>Enterobacter cloacae</i>.</p> <p>(b) (4)</p>
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<b>Duration of Treatment</b>	<p>The recommended dosage regimen of ZEMDRI is 15 mg/kg administered every 24 hours by intravenous (IV) infusion over 30 minutes in patients 18 years of age or older and with creatinine clearance [CLcr] greater than (b) (4) mL/min) up to 7 days (<i>see package insert for ails</i>).</p> <p><i>Also, see package insert for the recommended dosage in patients with varying degrees of renal function (b) (4)</i></p>
<b>Maximum Daily Dose</b>	As above ( <i>see the package insert for details</i> )
<b>Alternative Methods of Administration</b>	N/A

**B. Quality Assessment Overview**

The proposed drug substance, plazomicin sulfate, (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. (b) (4)

The only excipients in the formulation are sodium hydroxide, NF and Water for Injection, USP, which are both compendial. There are no novel excipients or excipients of human or animal origin in the drug product formulation.

The specification includes tests relevant for the proposed dosage form, such as appearance, identity, degradants, assay, pH, particulates, endotoxins, and sterility (or container-closure integrity). For the most part the analytical methods are compendial. (b) (4)

(b) (4) The HPLC method for assay and impurities is described in reasonable detail and has been validated. The HPLC method was verified by an FDA laboratory and found to be acceptable. Satisfactory batch analysis data are provided for 13 batches including three primary registration stability batches. A risk assessment has been performed for elemental impurities following the recommendations of ICH Q3D.

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.

Stability data for four batches manufactured by (b) (4) and three batches manufactured by (b) (4) have been provided in the NDA, with vials stored upright and inverted. This includes 24 months of long-term data at 5°C for three registration stability batches, manufactured at (b) (4) close to the commercial scale, submitted in the amendment dated May 4, 2018. There are no out of specification results. The main trends are towards higher levels of (b) (4), to a lesser extent (b) (4) and slight increases in the other degradants (and hence total impurities) with time and temperature. Eventually, a decrease in assay can be seen at accelerated conditions. In addition, supportive data, i.e., 24 months for an additional (b) (4) batch, 36 months for one (b) (4) batch, and 48 months for two (b) (4) batches were also adequate. Similar trends are seen for all batches with no obvious changes observed after freeze/thaw and photo stability testing. Initially, the proposed expiration dating of 36 months was not considered to be supported by the data available early in the NDA review cycle (i.e., only 18-month long-term data for three primary stability batches). However, with the 24-month stability update submitted in the May 4, 2018 amendment, the proposed expiration dating period of 36 months can be granted with the storage statement: "Store ZEMDRI injection, 500 mg/10 mL (50 mg/mL), refrigerated at 2°C - 8°C". The overall information submitted in the NDA was found to be acceptable by the Drug Product Reviewer.

The drug product (b) (4) plazomicin sulfate in water for injection, with sodium hydroxide used to adjust the pH of the solution to a target of 6.5. (b) (4)

The

overall information regarding the manufacturing process provided in the initial NDA submission and subsequent amendments was found acceptable by the Process Reviewer.

The sterilization of the drug product is performed using (b) (4). During the NDA review, several deficiencies and additional information was requested in several areas of microbiology, such as container closure integrity, the in-use microbial challenge study, description of the manufacturing facility and equipment used in the manufacturing of commercial batches, the routine environmental monitoring program, (b) (4) validation study, (b) (4) validation studies, and media fill simulations. These deficiencies were adequately addressed by submitting additional microbiology information via several NDA amendments. This included the results of container closure integrity using the helium-based leak testing method submitted in the April 26, 2018 amendment (reviewed in the Product Quality Microbiology Memorandum dated May 1, 2018). The overall product quality microbiology information provided in the initial NDA submission and subsequent amendments was found acceptable by the Microbiology Reviewer.

No biowaiver request was submitted (or required) for the proposed drug product, plazomicin injection, as the pharmacokinetic profile of plazomicin was characterized in clinical studies involving healthy subjects (being reviewed by the Office of Clinical Pharmacology). In addition, since the proposed drug product is an aqueous solution, the dissolution testing is not applicable. Therefore, a Biopharmaceutics review was not needed for this NDA.

The Applicant provided a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b). The EIC was noted (b) (4) and, thus, additional information was requested from the Applicant to support the claim. The subsequent additional information indicated that significant risk would only occur at levels > 1 ppb. The required statement of no extraordinary circumstances was also included. Therefore, the claim for an exclusion from an EA has been found acceptable.

(b) (4) is responsible for drug substance manufacturing, packaging, release testing and stability testing, (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. (b) (4) drug product manufacturer with a history of OAI and VAI inspection outcomes. The firm has demonstrated they are capable of manufacturing the proposed drug product and are now in compliance with CGMPs following an adequate response to the WL and (b) (4) inspectional concerns. Therefore, this site has been found acceptable for the proposed manufacturing operations under the current NDA; however, a post-approval inspection of this site is recommended (refer to the Facilities Chapter for details). Following a completion of the review of all facilities associated with the NDA, the Facilities Reviewer concluded that there are no outstanding issues that prevent

approval of this NDA. Therefore, the Facility Chapter was finalized on (b) (4) and recommended approval for the proposed manufacturing and testing facilities.



**C. Special Product Quality Labeling Recommendations** (*see labeling review*)

**D. Final Risk Assessment** (*see Attachment I*)

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**MICROBIOLOGY**[IQA Review Guide Reference](#)**Product Background:**

**NDA:** 210303

**Drug Product Name / Strength:** Plazomicin Injection 500 mg/10 mL (50 mg/mL)

**Route of Administration:** Intravenous

**Applicant Name:** Achaogen, Inc.

**Manufacturing Site:** [REDACTED] (b) (4)

**Method of Sterilization:** [REDACTED] (b) (4)

***Review Recommendation: Adequate***

***Theme (ANDA only): N/A***

***Justification (ANDA only): N/A***

***Review Summary:*** The drug product is a 50 mg/mL solution for intravenous injection, packaged as a 10 mL volume in a 10 mL vial. The drug product is [REDACTED] (b) (4)

[REDACTED] The application is recommended for approval.

**List Submissions Being Reviewed:** 10/25/2017, 1/11/2018, 2/23/2018, 3/9/2018, 3/23/2018

**Highlight Key Outstanding Issues from Last Cycle:** N/A

**Remarks:** The submission was provided in the eCTD format.

**Concise Description Outstanding Issues Remaining:** None.

**Supporting Documents:**

DMF [REDACTED] (b) (4)

**List Number of Comparability Protocols (ANDA only): N/A**

**S Drug Substance**

The drug substance (b) (4)

**P.1 Description of the Composition of the Drug Product**

(0001 Module 3.2.P.1, 3.2.P.1 Description and Composition of the Drug Product.pdf)

- **Description of drug product** – Plazomicin Injection 500 mg/10 mL (50 mg/mL) is a sterile, clear, colorless to yellow solution.
- **Drug product composition** –

Ingredient	Quantity per Vial	Concentration	Function
Plazomicin sulfate	500 mg <sup>a</sup>	50 mg/mL	Active ingredient
Sodium hydroxide	q.s.	q.s.	pH adjustment
Water for Injection	q.s. to 10 mL	Not applicable	Vehicle

q.s. = quantum sufficit.

<sup>a</sup> Quantity of freebase per 10 mL. (b) (4)

- **Description of container closure system** –  
(Module 3.2.P.2, 3.2.P.2.4 Container Closure System.pdf, page 2/12)

Component	Supplier	Clinical Trial Material	Clinical Trial Material/Commercial Use
Vial	<span style="background-color: #cccccc; padding: 0 20px;">(b) (4)</span>	<span style="background-color: #cccccc; padding: 0 20px;">(b) (4)</span>	<span style="background-color: #cccccc; padding: 0 20px;">(b) (4)</span>
Stopper	<span style="background-color: #cccccc; padding: 0 20px;">(b) (4)</span>	<span style="background-color: #cccccc; padding: 0 20px;">(b) (4)</span>	<span style="background-color: #cccccc; padding: 0 20px;">(b) (4)</span>
Seal	<span style="background-color: #cccccc; padding: 0 20px;">(b) (4)</span>	<span style="background-color: #cccccc; padding: 0 20px;">(b) (4)</span>	<span style="background-color: #cccccc; padding: 0 20px;">(b) (4)</span>

**Reviewer’s Assessment: Adequate**

The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

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## **2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1**

### **2.A. Package Insert**

(Module 1.14.1.2, Zemdri-USPI-Annotated.pdf)

Storage at 2-8°C.

Route of administration: Intravenous infusion of 15 mg/kg over 30 minutes every 24 hours. A post-dilution hold time of 24 hours at room temperature is indicated following dilution of the drug product in 0.9% sodium chloride Injection, USP or Lactated Ringer's Injection, USP to final concentrations ranging from 2.5 to 45 mg/mL. An in-use microbial challenge test was performed (See P.2.5).

Container: 10 mL (b) (4) vial

#### **Reviewer's Assessment: Adequate**

The applicant has met regulatory expectations with regard to the information related to issues of product quality microbiology that is provided in the product labeling.

***Post-Approval Commitments:***

For post-approval stability commitment, see P.8.2.

***List of Deficiencies:*** Not applicable.

***Primary Microbiology Reviewer Name and Date:*** Laura R. Wasil, PhD. 3/28/2018

***Secondary Reviewer Name and Date (and Secondary Summary, as needed):*** Stephen Langille, PhD. 3/30/2018



Laura  
Wasil

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Langille

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**BIOPHARMACEUTICS****Application Number:** NDA 210303**Drug Product Name / Strength:** Zemdri<sup>1</sup>(plazomicin) Injection, 500 mg/10 mL**Route of Administration:** Intravenous**Applicant Name:** Achaogen**List Submissions being reviewed:**

Original dated 10/25/2017

Seq.0002 dated 11/22/2017

**Background:**

Achaogen is seeking approval for plazomicin injection to be administered intravenously for the treatment of patients 18 years older with the complicated urinary tract infections and bloodstream infections caused by designated susceptible microorganisms. The Application received a Breakthrough Therapy designation.

**Drug Substance:**

Plazomicin sulfate (b) (4)

**Drug Product:**

The composition of the drug product includes the active ingredient, sodium hydroxide and water for injection. Plazomicin injection is a sterile aqueous solution; therefore, dissolution testing is not applicable for this proposed drug product.

**Biowaiver Request:**

Biowaiver Request is not submitted nor required. The Applicant characterized the pharmacokinetic profile of plazomicin in healthy subjects (Studies ACHN-490-001, -003, and -006). The Office of Clinical Pharmacology will review these studies.

**Bridging of Formulations:**

During the drug product development, drug product manufacturing site transferred across three sites: Phase 1/2 study was conducted with the drug product manufactured at (b) (4) (b) (4) one of the Phase 3 study is conducted with the drug product manufactured at (b) (4) and the other Phase 3 study is conducted with the drug products manufactured at (b) (4). Commercial drug product will also be manufactured at (b) (4). The review of the drug product manufacturing process of different sites will be reviewed by Quality Reviewer(s).

<sup>1</sup> The proposed name is under review by DMEPA

**Table 19: Drug Product Process Comparison**

(b) (4)



In conclusion, the involvement of the Division of Biopharmaceutics is not needed for this NDA.

➤ ***SIGNATURES***

***Primary Biopharmaceutics Reviewer Name and Date:***

Banu S. Zolnik, PhD 3/13/2018

Biopharmaceutics Reviewer  
Division of Biopharmaceutics-Branch 1  
Office of New Drug Products

***Secondary Reviewer Name and Date:***

Elsbeth Chikhale, PhD 3/13/2018

Acting Biopharmaceutics Lead  
Division of Biopharmaceutics-Branch 1  
Office of New Drug Products



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Chikhale

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# NDA 210303 Plazomicin for Injection

## Review of Common Technical Document-Quality (Ctd-Q) Module 1 Labeling & Package Insert

### 1. Package Insert

(a) “Highlights” Section (21CFR 201.57(a))

-----DOSAGE FORMS AND STRENGTHS-----

ZEMDRI (plazomicin) injection 500 mg/10 mL (50 mg/mL) is (b) (4)  
(b) (4) containing plazomicin sulfate equivalent to 500 mg plazomicin freebase.

Item	Information Provided in NDA	Reviewer’s Assessment
<b>Product title, Drug name (201.57(a)(2))</b>		
Proprietary name and established name	ZEMDRI (plazomicin)	Adequate
Dosage form, route of administration	Injection	Adequate
Controlled drug substance symbol (if applicable)	NA	
<b>Dosage Forms and Strengths (201.57(a)(8))</b>		
A concise summary of dosage forms and strengths and salt equivalency statement	ZEMDRI (plazomicin) injection 500 mg/10 mL (50 mg/mL) is <span style="background-color: #cccccc;">(b) (4)</span> containing plazomicin sulfate equivalent to 500 mg plazomicin freebase.	Recommend: ZEMDRI (plazomicin) injection 500 mg/10 mL (50 mg/mL) is <span style="background-color: #cccccc;">(b) (4)</span> . <span style="background-color: #cccccc;">(b) (4)</span> a single-dose vial containing <span style="background-color: #cccccc;">(b) (4)</span> plazomicin sulfate equivalent to 500 mg plazomicin freebase.

(b) “Full Prescribing Information” Section

## 2. DOSAGE AND ADMINISTRATION

### 2.5 Preparation of Solutions

ZEMDRI is supplied as a (b) (4) fliptop 10-mL vial that contains (b) (4) in 10 mL Water for Injection (concentration of 50 mg/mL). The appropriate volume of ZEMDRI solution (50 mg/mL) for the required dose should be diluted (b) (4). The compatible diluents (b) (4) below.

ZEMDRI does not contain preservatives. Aseptic technique must be followed in preparing the infusion solution. Discard (b) (4).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

### 2.6 Stability in Intravenous Fluids

After dilution, ZEMDRI solution for administration is stable for 24 hours at room temperature at concentrations of 2.5 to 45 mg/mL in the following solutions:

0.9% Sodium Chloride Injection, USP

Lactated Ringer’s Injection, USP

### 2.7 Drug Compatibility

Compatibility of ZEMDRI for administration with other drugs has not been established. ZEMDRI should not be mixed with other drugs or physically added to solutions containing other drugs. Other medications should not be infused simultaneously with ZEMDRI through the same IV line.

Item	Information Provided in NDA	Reviewer’s Assessment
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	See above	Generally adequate and supported by the data in the NDA. Suggest: vial that contains (b) (4) in 10 mL Water for Injection

**# 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))**

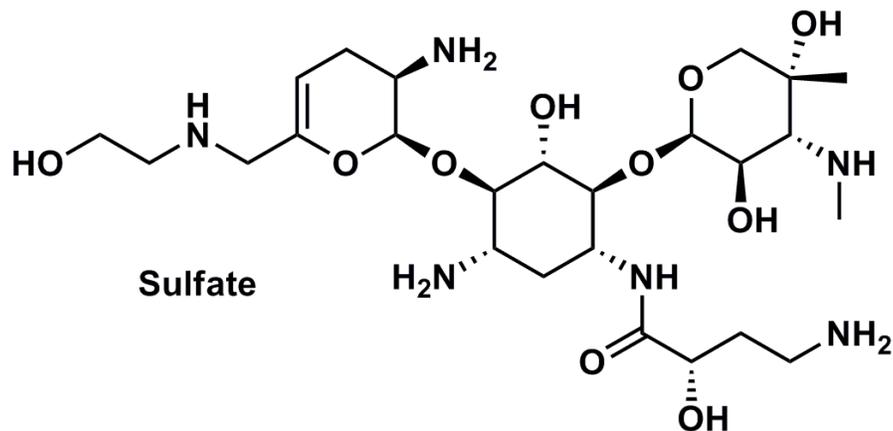
ZEMDRI injection 500 mg/10 mL (50 mg/mL) is (b) (4)  
 Each (b) (4) vial contains plazomicin sulfate equivalent to 500 mg plazomicin freebase (b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	ZEMDRI injection 500 mg/10 mL (50 mg/mL) (b) (4)	Recommend: ZEMDRI injection 500 mg/10 mL (50 mg/mL) is (b) (4) a clear colorless to yellow (b) (4) in a single-dose vial. (b) (4)
Strengths: in metric system and saltequivalency statement	500 mg/10 mL (50 mg/mL)	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable. Include "functional score", if present.	Each (b) (4) vial contains plazomicin sulfate equivalent to 500 mg plazomicin freebase (b) (4)	Recommend: Each single-dose (b) (4) vial contains (b) (4) plazomicin sulfate equivalent to 500 mg plazomicin freebase. (b) (4).

**#11: Description (21CFR 201.57(c)(12))**

(b) (4) a semi-synthetic aminoglycoside antibiotic derived from sisomicin.  
 (b) (4) chemical name is (2''R,3''R,4''R,5''R)-2''-[(1S,2S,3R,4S,6R)-4-amino-6-[(2''S)-4'''-amino-2'''-hydroxybutanamido)amino]-3-[(2'S,3'R)-3'-amino-6'-((2-hydroxyethylamino)methyl)-3',4'-dihydro-2H-pyran-2'-yloxy]-2-hydroxycyclohexyloxy]-5''-methyl-4''-(methylamino)tetrahydro-2H-pyran-3'',5''-diol sulfate. Plazomicin sulfate contains a theoretical 2.5 molar equivalents of sulfate relative to the freebase, based on complete protonation. The molecular weight of plazomicin sulfate is calculated based on 1:2.5 stoichiometry. The corresponding empirical formula is (b) (4) (plazomicin sulfate) and the molecular weight is (b) (4) g/mol.

**Figure 1: Chemical Structure of Plazomicin Sulfate**



ZEMDRI injection 500 mg/10 mL (50 mg/mL) is a clear, colorless-to-yellow liquid for <sup>(b) (4)</sup> administration supplied in 10-mL <sup>(b) (4)</sup> Type 1 glass vials. Each <sup>(b) (4)</sup> vial contains plazomicin sulfate equivalent to 500 mg plazomicin freebase at a concentration of 50 mg/mL adjusted to pH 6.5. Each mL also contains Water for Injection and sodium hydroxide for pH adjustment. This sterile, nonpyrogenic solution is formulated without preservatives.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	ZEMDRI; plazomicin	Adequate
Dosage form and route of administration	Injection	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	ZEMDRI injection 500 mg/10 mL (50 mg/mL) is a clear, colorless-to-yellow liquid for (b) (4) administration supplied in 10-mL (b) (4) Type 1 glass vials. Each (b) (4) vial contains plazomicin sulfate equivalent to 500 mg plazomicin freebase at a concentration of 50 mg/mL adjusted to pH 6.5. Each (b) (4) also contains Water for Injection and sodium hydroxide for pH adjustment. This sterile, nonpyrogenic solution is formulated without preservatives.	Recommend: ZEMDRI injection 500 mg/10 mL (50 mg/mL) is a clear, colorless-to-yellow liquid for (b) (4) administration supplied in 10-mL single-dose (b) (4) Type 1 glass vials. Each (b) (4) vial contains (b) (4) plazomicin sulfate equivalent to 500 mg plazomicin free base at a concentration of 50 mg/mL adjusted to pH 6.5. Each vial (b) (4) also contains Water for Injection and sodium hydroxide for pH adjustment. This sterile, nonpyrogenic solution is formulated without preservatives.
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	See above	
Statement of being sterile (if applicable)	Present	Adequate
Pharmacological/ therapeutic class	semi-synthetic aminoglycoside (b) (4)	Suggest: semi-synthetic aminoglycoside antibacterial
Chemical name, structural formula, molecular weight	Present	Adequate. Recommend: The chemical name of plazomicin sulfate (b) (4) is
If radioactive, statement of important nuclear characteristics.	NA	
Other important chemical or physical properties (such as pKa, solubility, or pH)	pH 6.5	Adequate

#### #16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

### 16.1 How Supplied

ZEMDRI injection 500 mg/10 mL (50 mg/mL) is supplied in (b) (4) 10-mL vials as a clear, colorless to yellow solution (b) (4). Each vial contains plazomicin sulfate equivalent to 500 mg plazomicin freebase at a concentration of 50 mg/mL plazomicin in Water for Injection. Each vial contains (b) (4) sodium hydroxide for pH adjustment to 6.5. The solution may become yellow in color; this does not indicate a decrease in potency.

NDC number	Package/Volume	Units per carton	plazomicin content
71045-010-02	Single use, fliptop vial, 10-mL	10	500 mg in 10 mL (50 mg/mL) (b) (4)

## 16.2 Storage and Handling

Store ZEMDRI injection 500 mg/10 mL (50 mg/mL) refrigerated at 2°C –8°C.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	500 mg/10 mL (50 mg/mL)	Adequate
Available units (e.g., bottles of 100 tablets). Include child-resistant closure, induction seal, coil, and desiccant as appropriate.	(b) (4) 10-mL vials	Recommend: single-dose (b) (4) 10-mL vials fitted with flip-off seals with royal blue polypropylene buttons
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number. Include "functional score", if present.	NDC number 71045-010-02 Package/Volume Single use, fliptop vial, 10-mL Units per carton 10 plazomicin content 500 mg in 10 mL (50 mg/mL)	Adequate. (b) (4) (b) (4) (b) (4)
Special handling (e.g., protect from light, do not freeze)	None	Adequate
Storage conditions	Store ZEMDRI injection 500 mg/10 mL (50 mg/mL) refrigerated at 2°C –8°C	Adequate

### Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Achaogen, Inc.	Needs some form of an address

## Overall Comments:

The suggested changes to the Package Insert described above have been added to the document on the clinical division's SharePoint site.



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## **NDA 210303 Plazomicin for Injection**

### **Container and Carton Labeling** (As modified in the Amendment of 3/14/18)

#### **1) Immediate Container Label**



#### **Text on label:**

**NDC 71045-010-01**

**[ZEMDRI™]**

(plazomicin) Injection

**500 mg/10 mL per vial\*      Rx ONLY**  
**(50 mg/mL)**

For Intravenous Infusion Only

Must dilute before use

**(b) (4)** vial

Discard unused portion

\*Contains plazomicin sulfate equivalent to 500 mg plazomicin, Water for Injection q.s., and sodium hydroxide for pH adjustment.

See package insert for complete instructions for use.

**Storage: Refrigerate at 2°C to 8°C (36°F to 46°F)**

**Manufactured for:** Achaogen, Inc.  
1 Tower Place

South San Francisco, CA 94080

APPEARS THIS WAY ON ORIGINAL

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	ZEMDRI™ (plazomicin) Injection	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4)) and salt equivalency statement (space permitting)	<b>500 mg/10 mL (50 mg/mL)</b>	Adequate
Route of administration 21.CFR 201.100(b)(3))	Injection	Adequate
Net contents (21 CFR 201.51(a))	<b>500 mg/10 mL</b>	Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)	Water for Injection q.s., and sodium hydroxide for pH adjustment	Adequate. Do we need q.s.?
Lot number per 21 CFR 201.18	Reserved place	Adequate
Expiration date per 21 CFR 201.17	Reserved place	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	Present	Adequate
Storage (not required)	Refrigerate at 2°C to 8°C (36°F to 46°F)	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	<b>NDC 71045-010-01</b>	Adequate
Bar Code per 21 CFR 201.25(c)(2)	Present	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	<b>Manufactured for:</b> Achaogen, Inc. 1 Tower Place South San Francisco, CA 94080	Adequate
Others	For Intravenous Infusion Only Must dilute before use (b) (4) vial Discard unused portion	Generally adequate but recommend "single-dose". Also the word (b) (4) should be added

	<p>*Contains plazomicin sulfate equivalent to 500 mg plazomicin, Water for Injection q.s., and sodium hydroxide for pH adjustment.</p> <p>See package insert for complete instructions for use.</p>	
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## 2) Carton Labeling



### Text on Carton:

NDC (b) (4)

**[ZEMDRI™]**

(plazomicin) Injection

**Rx ONLY**

(b) (4)

10 (10 mL) (b) (4) vials

**500 mg/10 mL (50 mg/mL)**

For intravenous infusion only. Must dilute before use.

**Dosage and Administration:** For intravenous infusion only. See package insert for complete instructions for use.

**Storage:** Refrigerate at 2°C to 8°C (36°F to 46°F).

**Manufactured for:** Achaogen, Inc.  
1 Tower Place  
South San Francisco, CA 94080

**CARTON:** Each carton contains 10 (10 mL) (b)(4) vials. Each vial contains plazomicin sulfate equivalent to 500 mg plazomicin, Water for Injection q.s., and sodium hydroxide for pH adjustment, for a total of 10 mL at a concentration of 50 mg plazomicin per mL.

**Note:** Prior to administration, parenteral drug products should be inspected visually for particulate matter.

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	<b>[ZEMDRI™]</b> (plazomicin) Injection	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2)) and salt equivalency statement	<b>50 mg/mL</b>	Adequate
Net contents (21 CFR 201.51(a))	<b>500 mg/10 mL</b> Each carton contains 10 (10 mL) (b) (4) vials.	Generally adequate. Recommend single-dose. 10 (10 mL) seems awkward
Lot number per 21 CFR 201.18	Space provided	Adequate
Expiration date per 21 CFR 201.17	Space provided	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[ 201.10(a), 21CFR201.100(d)(2)]	Water for Injection q.s., and sodium hydroxide for pH adjustment	<b>Recommend deleting q.s.</b>
Sterility Information (if applicable)	Not present	<b>Should be added. Recommend (b) (4) single-dose vial"</b>
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Rx only (b) (4)	Rx only is acceptable (b) (4)
Storage Conditions	Refrigerate at 2°C to 8°C (36°F to 46°F)	Adequate.
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Present	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Space provided	Adequate
Name of manufacturer/distributor	Achaogen, Inc., 1 Tower Place, South San	Adequate

	Francisco, CA 94080	
"See package insert for dosage information" (21 CFR 201.55)	See package insert for complete instructions for use.	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	Not present	<b>Acceptable</b>
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	For intravenous use only <b>Note:</b> Prior to administration, parenteral drug products should be inspected visually for particulate matter.	Adequate

**Overall Comments:**

Suggested changes to the Package Insert have been added to the SharePoint site.

**The following recommended changes apply to the container label.**

Delete q.s. in Water for Injection q.s.

Change (b) (4) vial" to (b) (4) single-dose vial"

**The following recommended changes apply to the carton.**

Change "Each carton contains 10 (10 mL) (b) (4) vials" to "Each carton contains (b) (4) single-dose vials."

Delete q.s. in Water for Injection q.s.



**George  
Lunn**

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**Balajee  
Shanmugam**

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**Attachment I: Risk Table**

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
		H, M, or L		Acceptable or Not Acceptable	
Assay, Stability. Impurities	Formulation, Process parameters Raw materials Container closure	L	Adequate acceptance criteria for impurities; Storage under refrigerated conditions	Acceptable	
Uniformity of Dose	Formulation, Process parameters Raw materials Container closure	L	Adequate in-process controls; Acceptable overfill in a vial	Acceptable	
Leachables (Rubber stopper)	Container closure	L	Acceptable data for primary stability studies	Acceptable	New stopper needs to be evaluated for extractables/ leachables
Sterility	Formulation, Process parameters Raw materials Container closure	H	Adequate process parameters for sterilizing  Container closure system is acceptable; integrity testing is performed.	Acceptable	
Particulate matter	Formulation, Process parameters Raw materials	M	Data consistent across batches and test included in the specification	Acceptable	
Labeling	Unusual instructions for the preparation of the infusion solution. The calculated volume of ZEMDRI is diluted to a constant volume of 50 mL. Thus, dilution is	M	Instructions in label are clear. Procedure accepted by clinical reviewer.	Acceptable	Changes in infusion solution preparation instructions in label (Section 2) should be carefully reviewed for clarity.

	inversely proportional to dose.				
Compatibility with infusion equipment	Materials for the infusion set might interfere with the infusion solution	M	A variety of different materials were tested for compatibility.  These are listed in the label.	Acceptable	Addition of new materials to the list of acceptable materials in the label should be supported by data (b) (4)
Facilities	<i>History of OAI and VAI inspection outcomes for drug product manufacturer,</i> (b) (4)	H	Current acceptable CGMP status	Acceptable	(b) (4)

OVERALL RECOMMENDATION:

This NDA is recommended for Approval from the Product Quality perspective. *The assessment of the (b) (4) will be documented via an OPQ Review Addendum.*

**On behalf of the OPQ Team**

Dorota Matecka, ATL for NDA 210303

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