

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### *APPLICATION NUMBER:*

**210303Orig1s000**

*Trade Name:* ZEMDRI 500 mg/10 mL per vial (50 mg/mL)

*Generic or Proper Name:* plazomicin

*Sponsor:* Achaogen, Inc

*Approval Date:* June 25, 2018

*Indication:* Treatment of Complicated Urinary Tract Infections (cUTI), including pyelonephritis, caused by the following susceptible microorganisms:

*Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, and Enterobacter cloacae, in patients 18 years of age and older.*

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## 210303Orig1s000

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*APPLICATION NUMBER:*

**210303Orig1s000**

**APPROVAL LETTER**



NDA 210303/Original-1

**NDA APPROVAL**

Achaogen, Inc.  
Attention: Anne Keane, PA-C, JD  
Senior Director, Head of Regulatory Affairs  
1 Tower Place, Suite 300  
South San Francisco, CA 94080

Dear Ms. Keane:

Please refer to your New Drug Application (NDA) dated October 25, 2017, received October 25, 2017, and your amendments submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ZEMDRI (plazomicin) Injection 500 mg/10 mL per vial (50 mg/mL).

NDA 210303 provides for the use of ZEMDRI (plazomicin) Injection for the following indications which, for administrative purposes, we have designated as follows:

- NDA 210303/Original 1-Treatment of Complicated Urinary Tract Infections (cUTI), including pyelonephritis, caused by the following susceptible microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Enterobacter cloacae*, in patients 18 years of age and older.

As only limited clinical safety and efficacy data for ZEMDRI are currently available, reserve ZEMDRI for use in cUTI patients who have limited or no alternative treatment options.

- NDA 210303/Original 2- Treatment of Bloodstream Infections caused by the following susceptible microorganism(s): *Klebsiella pneumoniae* and *Enterobacter aerogenes* in patients 18 years or older who have limited or no alternative treatment options.

The subject of this action letter is NDA 210303/Original-1. A separate action letter will be issued for NDA 210303/Original-2.

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

## **WAIVER OF HIGHLIGHTS SECTION**

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

## **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling text for the prescribing information. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible via publicly available labeling repositories.

## **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels, submitted on May 25, 2018, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 210303.**” Approval of this submission by FDA is not required before the labeling is used.

## **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric studies for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually

according to 21 CFR 314.81 and section 505B(a)(3)(C) of the FDCA. These required studies are listed below.

3393-1 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.

The timetable you submitted on June 22, 2018, states that you will conduct this study according to the following schedule:

Final protocol submission: Submitted  
Study/trial completion: 12/2019  
Final report submission: 06/2020

3393-2 Conduct a randomized active-controlled pharmacokinetic and safety trial of plazomicin in children ages birth to 18 years with cUTI including acute pyelonephritis.

The timetable you submitted on June 22, 2018, states that you will conduct this study according to the following schedule:

Draft protocol submission: 07/2018  
Final protocol submission: 12/2018  
Study/trial completion: 12/2022  
Final report submission: 06/2023

Submit the protocols to your IND 102563, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the serious risk of development of resistance to ZEMDRI in organisms specific to the cUTI indication in the label.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following study:

3393-3 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 timetable you submitted on June 22, 2018, states that you will conduct this study according to the following schedule:

Draft protocol submission:	06/2018
Final Protocol Submission:	08/2018
First interim report:	07/2019
Second interim report:	07/2020
Third interim report:	07/2021
Fourth interim report:	07/2022
Fifth interim report:	07/2023
Study completion:	09/2023
Final report submission:	12/2023

Submit clinical protocol to your IND 102563 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also, include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

**POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS  
UNDER SECTION 506B**

We remind you of your postmarketing commitments:

3393-4: Conduct a clinical study in subjects with end stage renal disease (ESRD) receiving hemodialysis to evaluate the pharmacokinetics of plazomicin.

The timetable you submitted on June 22, 2018 states that you will conduct this study according to the following schedule:

Draft protocol submission: 03/2019  
Final protocol submission: 06/2019  
Study/trial completion: 09/2020  
Final report submission: 03/2021

3393-5: 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 in patients with complicated urinary tract infections (cUTI).

As you stated in your correspondence dated June 22, 2018, you will support the submission of an application to FDA/CDRH according to the following schedule:

Final Submission to FDA/CDRH: September 25, 2018

Submit clinical protocols to your IND 102563 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **“Postmarketing Commitment Protocol,” “Postmarketing Commitment Final Report,”** or **“Postmarketing Commitment Correspondence.”**

**PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the prescribing information to:



OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the prescribing information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

### **MEDWATCH-TO-MANUFACTURER PROGRAM**

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

## **POST APPROVAL FEEDBACK MEETING**

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Christopher L. Smith PharmD, MPH, Regulatory Project Manager, at (301) 796-4851.

Sincerely,

*{See appended electronic signature page}*

Edward Cox MD, MPH  
Director  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure(s):

Content of Labeling  
Carton and Container Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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EDWARD M COX  
06/25/2018