CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210303Orig1s000

OTHER REVIEW(S)

Clinical Inspection Summary

Date	June 1, 2018
From	John Lee, M.D., Medical Officer Janice Pohlman, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Christopher Smith, Pharm.D., M.P.H., Regulatory Project Manager Shrimant Mishra, M.D., M.P.H., Medical Officer Dmitri Iarikov, M.D., Ph.D., Clinical Team Leader Sumati Nambiar, M.D., M.P.H., Director Division of Anti-Infective Products (DAIP)
Application	NDA 210303
Applicant	Achaogen, Inc.
Drug	Plazomicin (proposed, Zemdri®)
NME	Yes
Review Status	Priority
Proposed Indication	Treatment of complicated urinary tract infections (including pyelonephritis) or bloodstream infections in patients with limited or no alternative treatment options
Consultation Date	December 2, 2017
CIS Goal Date	June 4, 2018
Action Goal Date	June 25, 2018
PDUFA Due Date	June 25, 2018

I. OVERALL ASSESSMENT OF FINDINGS

Studies ACHN-490-007 and ACHN-490-009 were identified for on-site audit at good clinical practice (**GCP**) inspections of four foreign clinical investigator (**CI**) sites and the sponsor site. A Form FDA 483 was issued at Site 6801 (CI Michal Nowicki) in Study ACHN-490-009 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. For both studies at all inspected sites, study conduct appeared adequately GCP-compliant, including sponsor oversight of study conduct. All audited data were acceptably verifiable against source records and case report forms (**CRFs**). The data from the inspected sites appear reliable as reported in the NDA.

II. BACKGROUND

Achaogen, Inc. proposes plazomicin sulfate (pending trade name Zemdri®) to treat blood stream infection (**BSI**) or complicated urinary tract infections (**cUTIs**) including acute pyelonephritis (**AP**) with limited or no alternative treatment options. Plazomicin sulfate is a semisynthetic aminoglycoside antibiotic with structural modifications to its parent compound (sisomicin) that allow retention of antibiotic activity in the presence of bacterial enzymes that commonly inactivate currently marketed aminoglycosides and other antibiotics. Studies ACHN-490-007 and ACHN-490-009 were identified for on-site audit.

Study ACHN-490-007

A Phase 3, Multicenter, Randomized, Open Label Study to Evaluate the Efficacy and Safety of Plazomicin Compared with Colistin in Patients with Infection Due to Carbapenem-Resistant Enterobacteriaceae (CRE)

(b) (4)

Study ACHN-490-009

A Phase 3, Randomized, Multicenter, Double-Blind Study to Evaluate the Efficacy and Safety of Plazomicin Compared with Meropenem followed by Optional Oral Therapy for the Treatment of Complicated Urinary Tract Infection (cUTI), including Acute Pyelonephritis (AP), in Adults

This randomized, double-blind, non-inferiority study of plazomicin was conducted over 8 months in 2016 in 609 subjects at 68 CI sites in North America and Europe. The primary study objective was to demonstrate non-inferiority of plazomicin relative to meropenem (followed by optional oral therapy) in treating adults with cUTI using microbiologic eradication and clinical cure as co-primary endpoints, as analyzed for the microbiological modified intent-to-treat population. Randomization (equal ratio) was stratified by infection (cUTI or AP) and geographic region.

Adult subjects with a clinical diagnosis of cUTI (including AP) requiring at least 4 days of intravenous (**IV**) antibiotic therapy were enrolled. Subjects received either (dose adjusted for renal function): plazomicin 15 mg/kg over 30 minutes IV once daily followed by placebo infusions 8 and 16 hours later, or meropenem 1.0 gram over 30 minutes IV every 8 hours. After at least 4 days, the study medication could be switched to open-label oral levofloxacin 250 or 500 mg once daily (depending on renal function) or an acceptable alternative oral agent to complete 7-10 days of therapy (IV plus oral).

III. INSPECTION OUTCOMES

	Inspected Entity	Study / Site Enrollment	Dates	Outcome
1	Michal Nowicki, M.D. Pomorska 251 str. Lodz, Lodzkie 92-213, Poland	ACHN-490-009 Site 6801 21 subjects	March 19 – 23, 2018	VAI
2	Andrei Uksov, M.D. Meegomae Village, Voru Voru County 65526, Estonia	ACHN-490-009 Site 3204 28 subjects	March 26 – 29, 2018	NAI
3	Peter Tenke, M.D., Ph.D. Koves u. 1 Budapest H-1204, Hungary	ACHN-490-009 Site 4001 19 subjects	April 9 - 13, 2018	NAI
(b) (4)				
5	Achaogen, Inc. 1 Tower Place, Suite 300 South San Francisco, CA	(b) (4) ACHN-490-009 Sponsor		NAI

Site Selection: Sponsor or CI site with large subject enrollment, and in Study ACHN-490-009:

- Site 6801: high plazomicin safety (more AEs), inspected within 3 years
- Site 4001: high plazomicin efficacy, not inspected within 3 years
- Site 3204: high plazomicin efficacy, high meropenem safety (more AEs)

Compliance Classification of Inspection Outcome

NAI = No Action Indicated, no significant deviations from regulations
VAI = Voluntary Action Indicated, minor deviations from regulations
OAI = Official Action Indicated, major deviations from regulations

(b) (4)

1. Michal Nowicki, M.D.

21 subjects were screened, 21 were enrolled, and 16 completed the study. Case records were reviewed in detail for all subjects. Major NDA data listings were verified against on-site source records and CRFs: subject randomization, subject discontinuation, AEs, protocol deviations, major efficacy endpoints, and concomitant antibiotic medication use.

A Form FDA 483 was issued for inadequate study records, for inadequate documentation of training and task delegation for some study staff who administered the study medication. This finding appeared unlikely to be significant to the study outcome (blinding apparently maintained). Study conduct otherwise appeared GCP-compliant, including sponsor oversight of study conduct. All audited NDA data were adequately verifiable against source records and CRFs.

2. Andrei Uksov, M.D.

29 subjects were screened, 28 were enrolled, and 20 completed the study. Case records were reviewed in detail for all subjects. Major NDA data listings were verified against on-site source records and CRFs: subject randomization, subject discontinuation, AEs, protocol deviations, major efficacy endpoints, and concomitant antibiotic medication use.

No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct appeared GCP-compliant, including sponsor oversight of study conduct. All audited NDA data were adequately verifiable against source records and CRFs.

3. Peter Tenke, M.D., Ph.D.

19 subjects were screened, 19 were enrolled, and 13 completed the study. Case records were reviewed in detail for all subjects. Major NDA data listings were verified against on-site source records and CRFs: subject randomization, subject discontinuation, AEs, protocol deviations, major efficacy endpoints, and concomitant antibiotic medication use.

No significant deficiencies were observed and a Form FDA 483 was not issued. Verbal discussion included an isolated deficiency observation about not performing pregnancy testing for one subject as indicated per-protocol at end of intravenous study medication administration. Study conduct appeared GCP-compliant, including sponsor oversight of study conduct. All audited NDA data were adequately verifiable against source records and CRFs.

5. Achaogen, Inc.

This sponsor inspection consisted of: (1) general records review, to evaluate compliance with GCP regulations applicable to the sponsor, including internal data audit, database management, and systems validation; and (2) review of CI financial disclosure and CI site training/monitoring for (b) (4) ACHN-490-009, including detailed review of data reporting from the four CI sites linked to this sponsor inspection.

No significant GCP deficiencies were observed and a Form FDA 483 was not issued. There was no evidence of unblinding or biased data collection, and drug accountability records were adequate. The sponsor's oversight o (b) (4) ACHN-490-009 at the four inspected CI sites (linked with this sponsor inspection) appears to have been adequately GCP-compliant.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice K. Pohlman, M.D., M.P.H.
Team Leader
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Kassa Ayalew, M.D., M.P.H.
Branch Chief
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CC:

Central Document Room / NDA 210303
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DAIP / Clinical Team Leader / Dmitri Iarikov
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OSI / Database Project Manager / Dana Walters

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/s/

JONG HOON LEE
06/01/2018

JANICE K POHLMAN
06/01/2018

KASSA AYALEW
06/01/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 30, 2018

To: Shrimant Mishra, M.D.
Division of Anti-Infective Products (DAIP)

Christopher Smith, Regulatory Project Manager, (DAIP)

Abimbola Adebowale, Associate Director for Labeling, (DAIP)

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for ZEMDRI™ (plazomicin) Injection, for intravenous use

NDA: 210303

In response to DAIP's consult request dated April 12, 2018, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for ZEMDRI™.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAIP on May 21, 2018, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on May 25, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

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/s/

DAVID F FOSS
05/30/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 29, 2018
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 210303
Product Name and Strength:	Zemdri (plazomicin) for injection 500 mg/10 mL (50 mg/mL)
Applicant/Sponsor Name:	Achaogen, Inc.
FDA Received Date:	May 25, 2018
OSE RCM #:	2017-2190-4
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Anti-Infective Products (DAIP) requested that we review the revised container label and carton labeling for Zemdri (Appendix A) to determine if they if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container label and carton labeling (both with and without the Limited Population for Antibacterial Drugs (LPAD) language) for Zemdri are acceptable from a medication error perspective. We defer to DAIP regarding the appropriateness of approval under the LPAD pathway and therefore which container label and carton labeling (with and without the LPAD language) is to be approved.

[a] Myers, D. Label and Labeling Review Memo for Zemdri (NDA 210303). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAY 08. RCM No.: 2017-2190-3.

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/s/

DEBORAH E MYERS
05/29/2018

OTTO L TOWNSEND
05/29/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 8, 2018
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 210303
Product Name and Strength:	Zemdri (plazomicin) for injection 500 mg/10 mL (50 mg/mL)
Applicant/Sponsor Name:	Achaogen, Inc.
FDA Received Date:	April 19, 2018
OSE RCM #:	2017-2190-3
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Anti-Infective Products (DAIP) requested that we review the revised container label and carton labeling that include the proposed Limited Population for Antibacterial Drugs (LPAP) language, along with some minor changes (see Appendix A), for Zemdri to determine if they are acceptable from a medication error perspective. The Zemdri container label and carton labeling has previously been reviewed by DMEPA.[a,b,c]

2 CONCLUSION

The revised container label and carton labeling are unacceptable from a medication error perspective. We provide a recommendation to delete the hyphen that was added to the carton labeling. In addition, on behalf of the Office of Pharmaceutical Quality (OPQ), we provide a

[a] Myers, D. Label and Labeling Review for Zemdri (NDA 210303). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 FEB 01. RCM No.: 2017-2190.

[b] Myers, D. Label and Labeling Review Memo for Zemdri (NDA 210303). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 FEB 18. RCM No.: 2017-2190-1.

[c] Myers, D. Label and Labeling Review Memo for Zemdri (NDA 210303). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAR 148. RCM No.: 2017-2190-2.

recommendation to the Applicant to revise the package type term [redacted] (b) (4) "single-dose" on both the container label and carton labeling.

3 RECOMMENDATIONS FOR ACHAOGEN, INC.

We recommend the following be implemented prior to approval of NDA 210303:

Carton Label			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
1.	We note the product volume includes a hyphen between the number and mL (i.e., 10-mL). This is inconsistent with other areas of the container label and carton labeling in which the hyphen is not present between the number and mL (e.g., 10 mL).	Inconsistent labeling may contribute to confusion that can result in medication error.	For consistency, we recommend removal of the hyphen between the number and mL (i.e., 10-mL). For example, "10 (10 mL) vials Single…"
Container Label and Carton Labeling			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
1.	We note the use of the package type term, [redacted] (b) (4)	[redacted] (b) (4) is not considered an appropriate package type term.[d]	Change the package type term [redacted] (b) (4) to "single-dose."

[d] Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2015. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON APRIL 19, 2018

Two versions of the container label and carton labeling were submitted; one with and one without the LPAD language. In addition, the Applicant proposed the following minor changes:

- Linear barcode is included on the vial label
- "500 mg/10 mL per vial (50 mg/mL)" is listed on one line instead of two on the carton label
- A hyphen is included in "10 (10-mL) vials" on the carton label
- "(b) (4)" has been removed from the carton label

Container label (not to scale)

Without the LPAD language

(b) (4)

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/s/

DEBORAH E MYERS
05/08/2018

OTTO L TOWNSEND
05/08/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 19, 2018
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 210303
Product Name and Strength:	Zemdri (plazomicin) for injection 500 mg/10 mL (50 mg/mL)
Applicant/Sponsor Name:	Achaogen, Inc.
FDA Received Date:	March 14, 2018
OSE RCM #:	2017-2190-2
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Anti-Infective Products (DAIP) requested that we review the revised container label and carton labeling for Zemdri (plazomicin) (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during previous label and labeling reviews.[a,b]

2 CONCLUSION

The revised container label and carton labeling for Zemdri (plazomicin) are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Myers, D. Label and Labeling Review for Zemdri (NDA 210303). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 FEB 01. RCM No.: 2017-2190.

[b] Myers, D. Label and Labeling Review Memo for Zemdri (NDA 210303). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 FEB 18. RCM No.: 2017-2190-1.

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/s/

DEBORAH E MYERS
03/19/2018

OTTO L TOWNSEND
03/19/2018

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 14, 2018

TO: Debra B. Birnkrant, M.D.
Director, Division of Antiviral Products (DAVP)
Office of Antimicrobial Products
Office of New Drugs

Sumathi Nambiar, M.D., MPH
Director, Division of Anti-Infective Products (DAIP)
Office of Antimicrobial Products
Office of New Drugs

FROM: Stanley Au, Pharm.D., BCPS
Pharmacologist (Acting Team Lead)
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

Himanshu Gupta, Ph.D.
Staff Fellow
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Science

THROUGH: Seongeun Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

SUBJECT: Surveillance inspection of (b) (4) (b) (4)

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS), Office of Translational Sciences (OTS), conducted an analytical inspection at (b) (4) (b) (4) NDA 210303(plazomicin, also referred to as ACHN-490).

(b) (4)

For NDA 210303, based on the inspection findings, there were no data integrity issues for the plazomicin concentration data for studies ACHN-490-002, (b) (4) and ACHN 490-009 and the analytical data are acceptable. However, the review division should consider the OSIS discussion item regarding the carryover issue in determining whether the proposed plazomicin therapeutic drug monitoring recommendations are appropriate.

The final inspection classification is Voluntary Action Indicated (VAI).

Inspected Studies

(b) (4)

NDA 210303

Study Number: ACHN-490-002
Study Title: A double-blind, randomized, comparator-controlled study to assess the safety, efficacy, and pharmacokinetics of ACHN-490 injection administered intravenously (IV) in patients with complicated urinary tract infections (cUTI) or acute pyelonephritis (AP).
Dates of sample analysis: (b) (4)

(b) (4)

Study Number: ACHN-490-009
Study Title: A Phase 3, randomized, multicenter, double-blind study to evaluate the efficacy and safety of plazomicin compared with meropenem followed by optional oral therapy for the treatment of complicated urinary tract infection (cUTI), including acute pyelonephriti
Dates of analytical conduct: (b) (4)

Analytical site: (b) (4)

OSIS scientists Stanley Au and Himanshu Gupta audited the analytical portion of the above studies at (b) (4) (b) (4)

The inspection included examining the facilities and site operations, records for laboratory equipment, method validation and sample analyses, and interviews with the firm's management and staff.

At the conclusion of the inspection, we observed an objectionable condition and Form FDA 483 was issued to the analytical site. The Form FDA 483 observation (**Attachment 1**), the firm's response dated March 1, 2018 (**Attachment 2**), and the OSIS evaluation are presented below.

(b) (4)

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(b) (4)

Conclusion

An objectionable condition was observed during this inspection and Form FDA 483 was issued. The final inspection classification is Voluntary Action Indicated (VAI).

(b) (4)

For NDA 210303, there were no data integrity issues for the plazomicin data from ACHN-490-002, (b) (4) and ACHN-490-490-009. Based on this finding, the plazomicin concentration data is acceptable. However, OSIS recommends that the review division further evaluate the impact of the plazomicin assay carryover issue in reviewing the appropriateness of the proposed plazomicin therapeutic drug monitoring recommendations.

Studies using similar methods conducted between January 2011 and the end of the current surveillance interval can be further reviewed by the FDA without an inspection. However, for future applications, OSIS recommends that the review division request and evaluate information on reinjected analytical runs as discussed in this review to determine whether the Form FDA 483 observation affects the analytical data acceptability.

Final Classification

VAI [redacted] (b) (4)

cc:

OSIS/Kassim/Choe/Mitchell/Nkah/Fenty-Stewart/
OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au/Gupta
OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas

Draft: SA 3/7/2018, 3/8/2018, 3/12/2018, 3/14/2018
Edit: JC 3/7/2018, 3/14/2018

ECMS: Cabinets/CDER_OC/OSI/OSIS--Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL SITES/ [redacted] (b) (4) NDA 210303 [redacted] (b) (4)

OSI file number: 7773 (NDA 210303), [redacted] (b) (4)

FACTS: [redacted] (b) (4)

Attachment 1: Form FDA 483 observation
Attachment 2: Firm’s response to Form FDA 483 observation and discussion items
Attachment 3: Comparative tecovirimat concentration results for batches, 5, 10, 28, and 32.
Attachment 4: Example of the carryover calculation for individual plazomicin subject samples

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/s/

STANLEY AU
03/14/2018

HIMANSHU GUPTA
03/14/2018

SEONGEUN CHO
03/14/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum:	February 28, 2018
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 210303
Product Name and Strength:	Zemdri (plazomicin) for injection 500 mg/10 mL (50 mg/mL)
Applicant/Sponsor Name:	Achaogen, Inc.
FDA Received Date:	February 20, 2018
OSE RCM #:	2017-2190-1
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMO

The Division of Anti-Infective Products (DAIP) requested that we review the revised container label and carton labeling for Zemdri (plazomicin) (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container label and carton labeling are unacceptable from a medication error perspective. We note that our previous recommendations were not completely implemented as requested. Additionally, we have provided comments regarding Achaogen's plans to serialize the carton labeling to be compliant with impending regulations related to Drug Supply Chain and Security Act (DSCSA). We also provide recommendations regarding the proposed location of the linear bar code in relationship to the 2D data matrix barcode on the container label.

3 RECOMMENDATIONS FOR ACHAOGEN, INC.

[a] Myers, D. Label and Labeling Review for Zemdri (NDA 210303). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 FEB 01. RCM No.: 2017-2190.

We recommend the following be implemented prior to approval of this NDA 210303:

Container Label			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
1.	As previously requested in our 02 FEB 2018 recommendations, the route of administration is not included on the principal display panel (PDP) of the revised container label.	Medication errors could occur involving the wrong route of administration, as well as the risk of incorrectly administering the drug as an intravenous bolus.	As required by, 21 CFR 201.100(b)(3), relocate the statement "For Intravenous Infusion Only" to the PDP.
2.	As previously requested in our 02 FEB 2018 recommendations, the cautionary statement "Must dilute before use" is not included on the PDP of the revised container label.	Medication errors could occur if the product were to be administered without dilution as an intravenous bolus.	Relocate the cautionary statement "Must dilute before use" to the PDP. To provide adequate space for recommendations #1 and #2, you may consider moving the information, (b) (4) to the side panel and relocating the statements: "For Intravenous Infusion Only", "Must dilute before use", and "(b) (4) vial. Discard unused portion." to the PDP of the container label.
3.	As currently presented, the close proximity of the 2D "inventory control" barcode to the linear barcode could result in the inability of a hospital scanner to accurately read the linear barcode.	The barcode should be surrounded by enough white space to allow scanners to read the barcode properly in accordance with 21 CFR 201.25(c)(1)(i).	To provide sufficient white space surrounding the barcode, relocate the 2D "inventory control" barcode away from the linear barcode.
Carton Labeling			

	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
1.	As currently presented, the close proximity of the 2D "inventory control" barcode to the lot number and expiration date could result in healthcare providers misinterpreting the "inventory control" barcode as a 2D data matrix barcode that contains the NDC and other product information.	Healthcare providers may erroneously attempt to scan the 2D "inventory control" barcode. Failure for a scanner to read a barcode has resulted in medication errors because healthcare providers manually override warnings of barcode mismatches in their pharmacy software systems.	Consider moving the 2D "inventory control" barcode so that it is not in close proximity of the lot number and expiration date.

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/s/

DEBORAH E MYERS
02/28/2018

OTTO L TOWNSEND
02/28/2018

LABEL AND LABELING REVIEW

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

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	February 1, 2018
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 210303
Product Name and Strength:	Zemdri (plazomicin) for injection, 500 mg/10 mL (50 mg/mL)
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Achaogen, Inc.
Submission Date:	10/25/2017
OSE RCM #:	2017-2190
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF REVIEW

As part of the NDA approval process for Zemdri (plazomicin) for injection, 500 mg/10 mL (50 mg/mL), the Division of Anti-Infective Products (DAIP) requested that we review the proposed container label, carton labeling, and prescribing information to identify areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below includes the identified medication error issues with the submitted container label, carton labeling, and prescribing information, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Division of DAIP

Prescribing Information (PI)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
General Issues			

1.	We note the use of the package type term, "(b) (4)" in Sections 2.5, *Preparation of Solutions*, 3, *Dosage Forms and Strengths*, 11, *Description*, and 16.1, *How Supplied*.	(b) (4) is not considered an appropriate package type term.[a]	We defer to the Office of Pharmaceutical Quality (OPQ) to determine the appropriate package type term, (b) (4) "single-dose" to be used in the PI labeling. If OPQ determines that the package type term "single-dose" is correct and recommends its use in the PI labeling, this recommendation to use the package type term, (b) (4) " should also be made for the container label and carton labeling (also see "Container Label and Carton Labeling section of this table).
Highlights of Prescribing Information			
1.	We note the use of the symbol, ">"in the table for dosage adjustment in patients with renal impairment.	The symbols '<', '≤', '>', and '≥' are dangerous abbreviations that appear on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations because these symbols are often mistaken and used as opposite of intended. Use of these symbols in the Dosage and Administration sections of the Highlights and FPI, could lead to medication errors.	To provide clarity we recommend replacing the ">" symbols with their intended meaning "greater than."
Full Prescribing Information (FPI), Section 2.1, *Recommended Dosage*			

[a] Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2015. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf

1.	We note the use of the symbol, “>” in the title of “Table 1.”	Same as above.	To provide clarity we recommend replacing the “>” symbol with the intended meaning “greater than.”
FPI, Section 2.2, *Dosage Adjustment in Patients With Renal Impairment*			
1.	We note the use of the symbols, “>” and “≤”.	Same as above.	To provide clarity we recommend replacing the “>”and “≤” symbols with their intended meaning “greater than” and “less than or equal to” respectively.
FPI, Section 2.3, *Therapeutic Drug Management in cUTI Patients*			
1.	We note the use of the symbol, “>”.	Same as above.	To provide clarity we recommend replacing the “>” symbol with the intended meaning “greater than.”
(b) (4)			
FPI, Section 2.6, *Stability in Intravenous Fluids*			
1.	In the final concentration statement, we note that the numeral “2.5” does not include a unit of measurement (mg/mL).	The lower concentration (2.5) in the range could be missed or misinterpreted because it is not followed by the appropriate unit of measurement (mg/mL).	To provide clarity and minimize the risk for misinterpretation, add the unit of measurement, “mg/mL,” after the numeral “2.5.” For example, “2.5 mg/mL to 45 mg/mL.”
FPI, Section 3, *Dosage Forms and Strengths*			
1.	We note that the appropriate information to facilitate identification of the dosage form is not included.	Reference 21 CFR 201.57(c)(4)(ii)	We recommend that the description of identifying characteristics, “a clear, colorless to yellow solution” of the dosage form be added

			in accordance with 21 CFR 201.57(c)(4)(ii).
FPI Section 16.1, *How Supplied*			
1.	We note the inclusion of a (b) (4) however no proposed carton labeling was submitted for our review. On January 19, 2018, we emailed an Information Request (IR) to the Applicant requesting that they submit their proposed carton labeling (b) (4) for our review.	The Applicant responded to our IR on January 24, 2018 that (b) (4) was included erroneously in the draft PI and they do not intend to market (b) (4) .	Delete the second line of information in the Table associated with (b) (4)
FPI, Section 16.2, *Storage and Handling*			
1.	Currently the storage statement reads "Store ZEMDRI injection 500 mg/10 mL (50 mg/mL) refrigerated at 2°C-8°C."	The storage statement does not include temperature represented in the corresponding Fahrenheit measurement.	Add the corresponding temperature range in Fahrenheit in parentheses following the "2°C-8°C." In addition, to provide clarity we recommend replacing the hyphen with its intended meaning, "to." For example, "2°C to 8°C (36°F to 46°F)."
Container Label and Carton Labeling			
1.	We note that the statement "Discard Unused Portion" has not been included following the package type on the container label and carton labeling.	The entire contents of the vial could be given as a single dose or "saved" for future use; resulting in improper dose (overdose) or use of deteriorated drug product medication errors respectively.	If OPQ determines that it is appropriate to recommend a change to the package type term (b) (4) to "Single-Dose" we again defer to OPQ to determine the appropriateness of revising the statement "Single-Dose Vial" to read "Single-Dose Vial – Discard Unused Portion" on the container label and carton

			labeling. If OPQ determines that the statement "Single-Dose Vial – Discard Unused Portion" is appropriate, this recommendation to use the statement "Single-Dose Vial – Discard Unused Portion" should also be made for the container label and carton labeling.

Table 3: Identified Issues and Recommendations for Achaogen, Inc. (entire table to be conveyed to Applicant)

Container Label and Carton Labeling			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
1.	The proprietary name is currently denoted by the placeholder "[TRADENAME®]."	The proposed proprietary name "Zemdri" was found conditionally acceptable on December 14, 2017.	Remove by the placeholder "[TRADENAME®]" and replace with the conditionally acceptable name "Zemdri."
2.	As currently presented the storage statement reads "Refrigerate at 2-8°C (36-46°F)" and is inconsistent with storage statement in the Full Prescribing Information (FPI), Section 16.1, *How Supplied*.	The units of measurement following the first numbers in the temperature range (e.g., degree and Centigrade symbols (°C) following the number 2 and degree and Fahrenheit symbols (°F) following the number 36) are missing.	Add the degree and Centigrade symbols (°C) following the number 2 and degree and Fahrenheit symbols (°F) following the number 36 within the storage statement for clarity. In addition, to provide further clarity we recommend replacing the hyphens with their intended meaning, "to." For example, "2°C to 8°C (36°F to 46°F)."
3.	As currently presented the storage statement font is not bolded.	Degradation of the product due to improper storage if the storage information is overlooked.	Bold the storage statement to increase the prominence of this important information. For example, "**Storage: Refrigerate at 2°C to 8°C (36°F to 46°F).**"

4.	As currently presented the route of administration is not included on the principal display panel (PDP).	Medication errors could occur involving the wrong route of administration, as well as the risk of incorrectly administering the drug as an intravenous bolus.	As required by, 21 CFR 201.100(b)(3), add the statement "For Intravenous Infusion Only" to the PDP.
5.	As currently presented the cautionary statement "Must dilute before use" is not included on the PDP.	Medication errors could occur if the product were to be administered without dilution as an intravenous bolus.	Add the cautionary statement "Must dilute before use" on the PDP.
Container Label Only			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
1.	As currently presented the "Rx Only" statement is competing in size with, as well as crowding the product strength.	The "Rx Only" statement should not appear more prominent than or crowd important safety information (i.e., product strength) on the principal display panel (PDP).	Decrease the prominence of and relocate the "Rx Only" statement away from the product strength.
2.	A linear barcode is not currently included.	The barcode is an important safety feature that should be part of the label whenever possible. Reference 21CFR 201.25(c)(2)	Add the product barcode as required per 21CFR 201.25(c)(2). Additionally, we recommend that the barcode be oriented in the vertical position to improve scannability, as barcodes placed in a horizontal position may not scan due to the curvature of the container.

4 CONCLUSION

DMEPA's evaluation of the proposed container label, carton labeling, and prescribing information identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 3 above and ask that the Division conveys the entire table to Achaogen, Inc. so that our recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED
APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Zemdri that Achaogen, Inc. submitted on October 25, 2017.

Table 4. Relevant Product Information for Zemdri	
Initial Approval Date	N/A
Active Ingredient	plazomicin
Indication	(b) (4) [redacted]
Route of Administration	Intravenous (IV)
Dosage Form	Solution for injection
Strength	500 mg/10 mL (50 mg/mL)
Dose and Frequency	15 mg/kg every 24 hours by intravenous (IV) infusion over 30 minutes in patients 18 years of age or older with creatinine clearance greater than (b) (4) mL/min. (b) (4) [redacted] (b) (4) [redacted]

	(b) (4)
How Supplied	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; this does not indicate a decrease in potency. The product is packaged as 10 units per carton.
Storage	Refrigerate at 2°C-8C° (36°F-46°F).
Container Closure	10-mL glass vial, rubber stopper and aluminum seal with a flip-off plastic button top

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On January 18, 2018, we searched the L:drive and AIMS using the terms, Zemdri to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified two previous reviews[b,c] involving review of the proposed proprietary name, Zemdri.

[b] Myers, D. Proprietary Name Review for Zemdri (IND 102563). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUN 13. RCM No.: 2017-12915039.

[c] Myers, D. Proprietary Name Memorandum for Zemdri (NDA 210303). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 DEC 11. RCM No.: 2017-18652866.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Zemdri labels and labeling submitted by Achaogen, Inc. on October 25, 2017.

- Container label
- Carton labeling
- Prescribing Information – available at the following link: \\cdsesub1\evsprod\nda210303\0001\m1\us\plazomicin-uspi-clean.docx

F.2 Label and Labeling Images

- Container label (not to scale)

(b) (4)

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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