CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211109Orig1s000

OTHER REVIEW(S)

MEMORANDUM

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:	August 16, 2018
Requesting Office or Division:	The Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 211109
Product Name and Strength:	Xerava (eravacycline) for injection; 50 mg/vial
Applicant/Sponsor Name:	Tetraphase Pharmaceuticals, Inc
FDA Received Date:	August 15, 2018
OSE RCM #:	2018-41-3
DMEPA Safety Evaluator:	Sevan Kolejian, PharmD, 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 Xerava (eravacycline) for injection; 50 mg per vial (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to DAIP's request for the Applicant to revise the salt equivalency statement from (b) (4) to "Each vial contains 50 mg eravacycline (equivalent to 63.5 mg of eravacycline dihydrochloride…" that was communicated via email on August 13, 2018.

2 CONCLUSION

The revised container label and carton labeling for Xerava (eravacycline) for injection; 50 mg per vial are acceptable from a medication error perspective.

We have no further recommendations at this time.

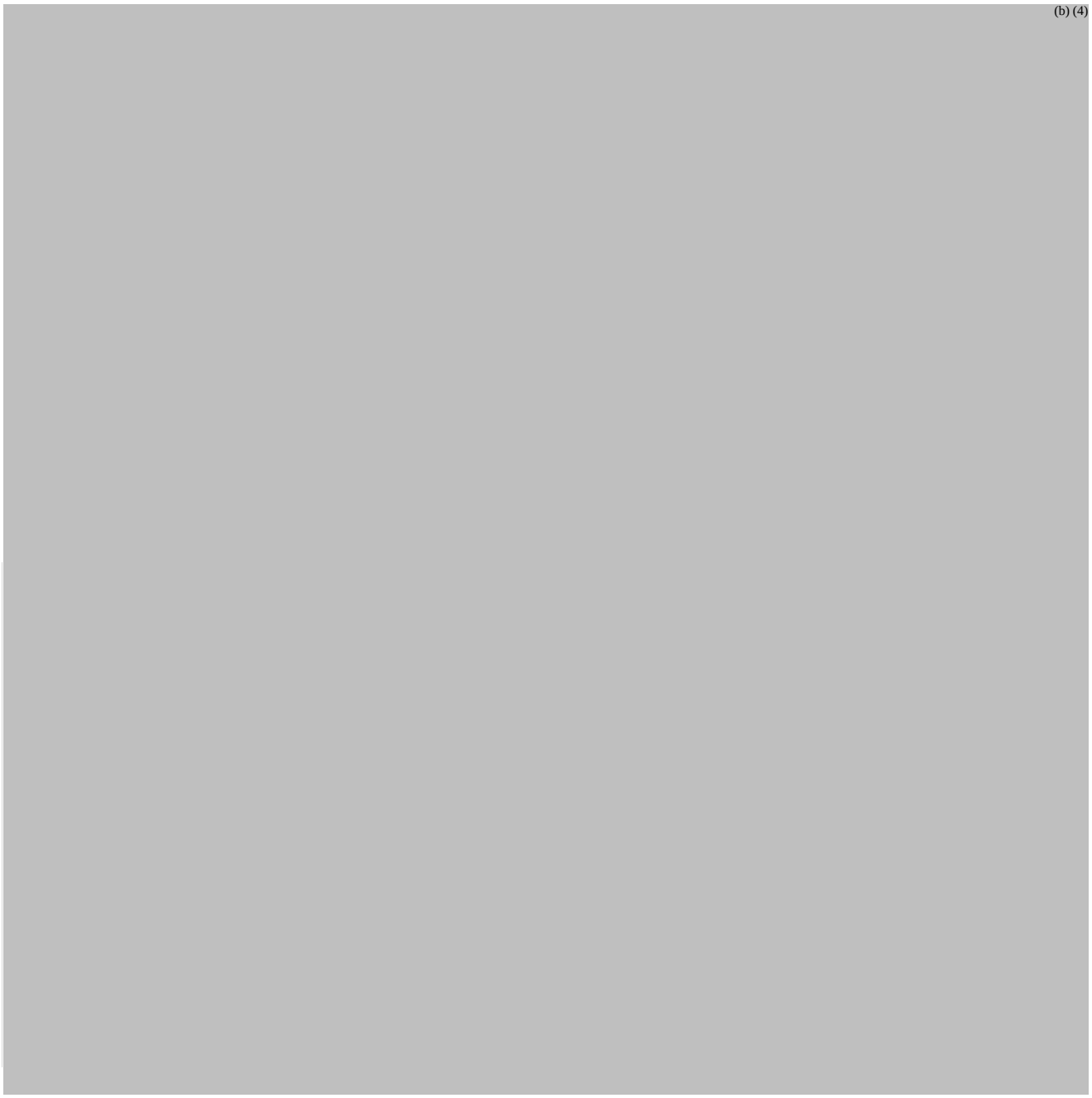
APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON AUGUST 15, 2018

1. Container labels

(b) (4)

2. Carton labeling

(b) (4)



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/s/

SEVAN H KOLEJIAN
08/16/2018

OTTO L TOWNSEND
08/16/2018

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

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

Memorandum

Date: July 31, 2018

To: Mark Needles, M.D.
Division of Anti-Infective Products (DAIP)

Gregory DiBernardo, 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 XERAVA (eravacycline) for injection, for intravenous use

NDA: 211109

In response to DAIP consult request dated March 6, 2018, OPDP has reviewed the proposed product labeling (PI), and carton and container labeling for the original NDA submission for XERAVA.

PI: OPDP's comments on the proposed labeling are based on the draft received by electronic mail from DAIP on July 24, 2018, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DAIP on July 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.

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

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/s/

DAVID F FOSS
07/31/2018

Clinical Inspection Summary

Date	06 July 2018
From	Aisha P. Johnson, MD, MPH, MBA, Medical Officer Janice Pohlman, MD, Clinical Team Leader Kassa Ayalew, MD, M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Mark Needles, MD, Clinical Reviewer Ed Weinstein, MD, Cross Discipline Team Leader Greg DiBernardo, RPM Division of Anti-Infective Products (DAIP)
NDA/BLA #	211109
Applicant	Tetraphase Pharmaceuticals, Inc.
Drug	Eravacycline powder for injection (b) (4)
NME (Yes/No)	Yes
Therapeutic Classification	Tetracycline
Proposed Indication(s)	Treatment of adult patients with complicated intra-abdominal infections (cIAI)
Consultation Request Date	23 February 2018
Summary Goal Date	15 July 2018
Action Goal Date	28 August 2018
PDUFA Date	28 August 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four clinical sites (Drs. Ruxanda, Gardovskis, Gurlich, and Chock) and the sponsor (Tetraphase Pharmaceuticals Inc.) were selected by the Division of Anti-Infective Products (DAIP) for inspection, in support of NDA 211109.

The preliminary CDER regulatory classification for the clinical sites is No Action Indicated (NAI). Clinical site observations noted below are based on the communications with the field investigators. A clinical inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

The final classification for the Tetraphase Pharmaceuticals, Inc. inspection is NAI.

The study data derived from these clinical sites and the sponsor are considered reliable in support of the requested indication.

II. BACKGROUND

Tetraphase Pharmaceuticals, Inc., is the NDA sponsor for eravacycline, a novel synthetic broad-spectrum fluorocycline belonging to the tetracycline class of antibiotics that is highly active against clinically important multi-drug resistant Gram-negative and Gram-positive aerobic and anaerobic pathogens. The proposed indication for eravacycline is the treatment of complicated intra-abdominal infection (cIAI) in adults. Intra-abdominal infection (IAI) is a broad term that is used to describe several processes, including (but not limited to) peritonitis, diverticulitis, cholecystitis, cholangitis, appendicitis, and pancreatitis. Complicated IAI (cIAI) is defined by the Infectious Diseases Society of America (IDSA) as an infection that extends beyond the wall of a hollow viscus of origin into the abdominal cavity while being associated with an abscess or peritonitis.[1]

The proposed eravacycline dosing regimen for the treatment of cIAI is 1.0 mg/kg every 12 hours for 4 to 14 days by intravenous (IV) infusion over 60 minutes.

Study TP-434-008
A Phase 3, Randomized, Double-Blind, Double-Dummy, Multicenter Prospective Study to Assess the Efficacy and Safety of Eravacycline Compared With Ertapenem in Complicated Intra-Abdominal Infections

This Phase 3, randomized, double-blind, double-dummy, multicenter study evaluated the non-inferiority (NI) of eravacycline 1.0 mg/kg IV q12h to ertapenem 1.0 g IV q24h in subjects with cIAI. The study population included patients hospitalized for cIAI requiring surgery or percutaneous drainage, with evidence of a systemic inflammatory response, and abdominal or flank pain or referred pain caused by cIAI. Eligible subjects could not have received effective antibacterial drug therapy for their current infection for more than 24 hours during the 72 hours preceding enrollment (including ertapenem or any other carbapenem or tigecycline). Subjects with documented cIAI (i.e., known baseline pathogen) who had received at least 72 hours of antibiotic therapy and were considered treatment failures could also be enrolled.

A total of 541 subjects were randomized (1:1) to receive either eravacycline 1.0 mg/kg every 12 hours (270 subjects) or ertapenem 1.0 g every 24 hours (271 subjects). This multicenter study was conducted at 66 sites in 11 countries (Bulgaria, Czech Republic, Estonia, Germany, Latvia, Lithuania, Romania, Russia, South Africa, and United States). Of the 541 subjects enrolled, only 38 (18 eravacycline, 18 ertapenem) were enrolled from sites in the United States. The geographic region with the highest number of subjects enrolled was Eastern Europe.

The primary endpoint was clinical response at the test of cure (TOC) visit. Clinical response was classified as cure, failure, or indeterminate based on pre-defined clinical outcome criteria.

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[1] Solomkin JS, Mazuski JE, Bradley JS. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50:133-164.

The first subject was enrolled 28 August 2013 and the last subject completed the study 26 August 2014.

Study:TP-434-025
A Phase 3, Randomized, Double-Blind, Double-Dummy, Multicenter, Prospective Study to Assess the Efficacy and Safety of Eravacycline Compared With Meropenem in Complicated Intra-Abdominal Infections

This Phase 3, randomized, double-blind, double-dummy, multicenter study evaluated the NI of eravacycline 1.0 mg/kg IV q12h to meropenem 1.0 g IV q8h in subjects with cIAI. The choice of the 1.0 mg/kg q12 dose regimen of eravacycline was made based on the positive outcome of Study TP-434-008.

A total of 500 subjects were randomized (1:1) to receive eravacycline 1.0 mg/kg every 12 hours (250 subjects) or meropenem 1g every 8 hours (250 subjects). This multicenter study was conducted at 65 sites in 11 countries: 8 in Bulgaria, 5 in Czech Republic, 4 in Estonia, 6 in Georgia, 3 in Hungary, 4 in Latvia, 5 in Lithuania, 9 in Romania, 9 in Russia, 10 in Ukraine, and 2 in United States). Of the 500 subjects enrolled, only 12 (8 eravacycline, 4 meropenem) were enrolled from sites in the United States.

The primary endpoint in the cIAI studies was clinical response at the TOC visit. Clinical response was classified as cure, failure, or indeterminate based on pre-defined clinical outcome criteria.

The first subject was enrolled 13 October 2106 and the last subject completed the study 19 May 2017.

III. RESULTS (by site):

Name of CI, Site #, Address, Country if non-U.S. or City, State if U.S.	Protocol # and # of Subjects	Inspection Date	Classification
Ruxanda, Anca Ileana 1 Tabaci St. Craiova, 200642 Romania Site Number 72	Protocol: TP-434-008 35 Subjects	May 14-18, 2018	NAI*
Gardovskis, Janis P. Stradins Clinical University Hospital, Surgery Clinic Pilsonu str. 13 Riga, Latvia -1002 Site number 81	Protocol: TP-434-025 34 Subjects	May 14-18, 2018	NAI*

Name of CI, Site #, Address, Country if non-U.S. or City, State if U.S.	**Protocol # and # of Subjects**	**Inspection Date**	**Classification**
Gurlich, Robert Srobarova 1150/50 Prague, 100 34 Czech Republic Site number 118	Protocol TP-434-025 10 subjects	May 21-24, 2018	NAI*
Chock, Stefan 3186 South Maryland Parkway Las Vegas, NV 89169 Site number 107	Protocol TP-434-008 17 subjects Protocol TP-434-025 7 subjects	May 30-June 8, 2018	NAI*
Sponsor Tetraphase Pharmaceuticals, Inc. 480 Arsenal Way, Suite 110 Watertown, MA 02472	Protocol:TP-434-008 Protocol:TP-434-025	June 4-8, 2019	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Brief Rationale for Sites selected for inspection:

- Dr. Ruxanda's site (#72) was selected due to high enrollment, high treatment efficacy (for serious infections) in both treatment arms and high evaluability rates (low occurrence of protocol violations).
- Dr. Gardovskis's site (#81) was selected due to high enrollment, high treatment efficacy rates, and relatively scant reporting of protocol violations and AEs
- Dr. Gurlich's site (#118) was selected due to participation in both studies and higher number of AEs and SAEs in the study treatment arm in Study 025. Inspection of Study 008 was to be done if time permitted.
- Dr. Chock's site (#107) was selected due to participation in both studies and was chosen as representative US site.
- Tetraphase Pharma was selected given that the current application is an NME and the sponsor is relatively small and has not been the subject of a previous inspection.

1. **Anca Ileana Ruxanda**/Site #72/Protocol TP-434-008

At this site, there were 37 subjects screened, 35 subjects enrolled, and 34 subjects completed the study. One subject discontinued the study due to death. There were 16 subject records reviewed.

The records reviewed included: informed consents; protocol amendments; signed investigator agreement, Financial Disclosure Statements; IRB submissions and correspondence; adverse events reporting; subject clinical evaluations; investigational drug product accountability and monitoring; concomitant medications; and sponsor monitoring activities.

The source records were reviewed and there were no discrepancies with the sponsor data line listings. There was no evidence of under-reporting of adverse events.

The ORA field investigator noted that two subjects blood cultures were not repeated until negative.

> OSI Reviewer comment:
> This finding was discussed with the ORA field inspector. Each of the two subjects had one of two bottles positive for organisms consistent with contaminants (Subject # (b) (6) with *Staphylococcus hominis* and # (b) (6) with *Streptococcus sanguinis*). Although the protocol required repeat blood cultures when initial culture positive, the clinician considered these to be contaminants and did not repeat the cultures.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

2. **Janis Gardovskis**/Site 81/Protocol TP-434-025

At this site, there were 35 subjects screened, 34 subjects enrolled, and 33 subjects completed the study. Subject (b) (4) experienced an adverse event and subsequently withdrew from the study. All subject randomization and informed consent forms were reviewed. A total of 16 subject charts were reviewed in depth.

The records reviewed included: informed consents; protocol amendments; signed investigator agreement, Financial Disclosure Statements; IRB submissions and correspondence; adverse events reporting; subject clinical evaluations; investigational drug product accountability and monitoring; concomitant medications; and sponsor monitoring activities.

The source records were reviewed and there were no discrepancies with the sponsor data line listings. The primary efficacy endpoint data was verifiable. There was no evidence of under-reporting of adverse events.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

3. **Robert Gurlich**/Site #18/Protocol TP-434-025

At this site, there were 10 subjects screened, 10 subjects enrolled, and eight subjects completed the study. One subject died and one subject withdrew from the study. This patient experienced an adverse event and was hospitalized. The patient left the hospital against medical advice.

The records reviewed included: informed consents; protocol amendments; signed investigator agreement, Financial Disclosure Statements; IRB submissions and correspondence; adverse events reporting; subject clinical evaluations; investigational drug product accountability and monitoring; concomitant medications; and sponsor monitoring activities.

The source records were reviewed and there were no discrepancies with the sponsor data line listings. The primary efficacy endpoint data was verifiable. There was no evidence of under-reporting of adverse events.

The inspection revealed adequate adherence to the regulations and the investigational plans. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, was issued.

4. Stefan Chock/Site 107/Protocols TP-434-025 and TP-434-008

For Protocol TP-434-025, there were 18 subjects screened, 17 subjects enrolled, and 14 subjects completed the study. There were two subjects lost to follow-up and one death.

For Protocol TP-434-008, There were eight subjects screened, seven subjects enrolled, and seven subjects completed the study.

At both sites, the records reviewed included: informed consents; protocol amendments; signed investigator agreement, Financial Disclosure Statements; IRB submissions and correspondence; adverse events reporting; clinical evaluations; investigational drug product accountability and monitoring; concomitant medications; and sponsor monitoring activities.

At both sites, the source records were reviewed and there were no discrepancies with the sponsor data line listings. The primary efficacy endpoint data was verifiable.

The following record keeping issues were discussed with the PI:

a. Subjects' dosing times were not assessed within the 24-hour *Study Drug Infusion Scheme* Dosing Cycle: Test Drug – *Eravacycline* 60 mins (+/-10 mins) and Placebo 30 mins (+/-5 mins)
b. Subjects' Oral Temperature - Not assessed consistently within 8 hours (+/-1 Hour)
c. Staff Authorization and Signature Log – Missing "End Dates" of study staff participation
d. Concomitant Medication Form – Missing PI's review/signature

e. Lack of Training Documentation (e.g. drug dosing times, 8-hour temperature times) demonstrating retraining conducted, attendees, identifying root cause, and assessing effectiveness of training)
f. Numerous overwrites throughout the source documents

Despite the record keeping issues listed above, the inspection revealed adequate adherence to the regulations and the investigational plans. The record-keeping issues did not have a significant effect on endpoint assessment. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

5. Tetraphase Pharmaceuticals, Inc.
480 Arsenal Way, Suite 110
Watertown, MA 02742

The inspection of the Sponsor included, but was not limited to, review of the organizational charts, standard operating procedures, monitoring plans, select monitoring reports, transfer of obligations, correspondence, training records, FDA 1572s, financial disclosure forms, electronic case report forms (eCRFs), safety plans, serious adverse events, and test article accountability records. For Study TP-434-008, data in the eCRF was compared against the data listings for clinical cure at the test of cure (TOC) visit for all subjects from Sites 72, 107, and 118. For Study TP-434-025 eCRF data was compared against the data listings for clinical cure at end of treatment (EOT), TOC, and follow up (FU) for all subjects from Sites 81, 107, and 118.

The contract research organization (CRO) used for the studies was (b) (4) Tetraphase approved all study plans. Meetings between Tetraphase and (b) (4) were held weekly while the studies were ongoing. Clinical investigators were selected by (b) (4) and approved by Tetraphase. The monitoring and medical monitoring plans for Study TP-434-008 were not approved at the time the first subject was enrolled. The first subject was enrolled on Aug 28, 2013 (randomized and dosed). However, the monitoring and medical monitoring plans were not finalized until 04 November 2013 and 19 November 2014, respectively. The monitoring and medical monitoring plans for Study TP-434-025 were approved prior to enrollment of the first subject.

Pharmacovigilance services were provided by (b) (4) was responsible for preparation of initial and follow-up IND safety reports. Tetraphase reviewed the reports and was responsible for approval and submission to FDA.

A (b) (4) was used for TP-434-008. Tetraphase selected and approved three (b) (4) members who had previously worked with Tetraphase during Phase 2 studies. One additional member was identified by (b) (4) and another was identified by an outside consultant. Their qualifications and credentials were reviewed and approved by Tetraphase. There was one version of the

(b) (4) charter with an effective date of (b) (4). No change in study conduct was recommended after the first two scheduled meetings and the third meeting was subsequently cancelled. No (b) (4) was used for Study TP-434-025.

There were two minor discussion items included in the meeting with management held at the close of the inspection:

a. Operational plans for Study IP-434-008, such as the final monitoring plan and medical monitoring plan, were not approved prior to the start of the study.
b. Monitoring reports were not always written by the monitors within 7 days of the monitoring visit and approved by the CRO within 10 days, as mandated by the monitoring plans.

Despite the discussion items described above, the inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

{See appended electronic signature page}

Aisha P. Johnson, MD, MPH, MBA
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H..
Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {*See appended electronic signature page}*

Susan D. Thompson, M.D., Team Leader, for
Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Doc. Rm.
Review Division /Division Director/
Review Division /Medical Team Leader/
Review Division /Project Manager/
Review Division/MO/
OSI/Office Director/
OSI/DCCE/ Division Director/
OSI/DCCE/Branch Chief/
OSI/DCCE/Team Leader/
OSI/DCCE/GCP Reviewer/
OSI/ GCP Program Analysts/
OSI/Database PM/Dana Walters

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/s/

AISHA P JOHNSON
07/06/2018

JANICE K POHLMAN
07/06/2018

SUSAN D THOMPSON
07/06/2018

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: June 19, 2018

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Gregory DiBernardo, RPM
DAIP

Subject: QT-IRT Consult to NDA 211109

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 05/01/2018 regarding the sponsor's QT related labeling proposal. The QT-IRT reviewed the following materials:

- Sponsor's proposed labeling; and
- Previous QT-IRT review under IND 104839 dated 08/07/2014 in DARRTS.

1. QT-IRT Responses

The Sponsor included the following language in the proposed label:

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

.

The following is QT-IRT's proposed labeling language, which is a suggestion only. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of eravacycline on the QTc interval was evaluated in a Phase 1 randomized, placebo and positive controlled, double-blind, single-dose, crossover thorough QTc study in 60 healthy adult subjects. At a single dose 1.5-fold of the recommended (b) (4) dose, eravacycline did not prolong the QTc interval to any clinically relevant extent.

2. BACKGROUND

Product Information

Eravacycline (TP-434) is an antibiotic of the tetracycline class. The proposed therapeutic dose is 1 mg/kg by IV infusion over 60 minutes every 12 hours for 4 to 14 days total duration. There is no accumulation in C_{max} with multiple dosing.

Excerpt from the previous QT-IRT review for the TQT study

No significant QTc prolongation effect of a single IV dose of eravacycline 1.5 mg/kg was detected in the TQT study. In this randomized, blinded, three-period crossover study, 60 healthy subjects received a single IV dose of eravacycline 1.5 mg/kg, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1:The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bound for Eravacycline 1.5 mg/kg and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
Eravacycline 1.5 mg/kg	3	3.7	(1.5, 5.9)
Moxifloxacin 400 mg*	2	12.0	(9.1, 14.9)

* Multiple endpoint adjustment of 3 time points was applied.

There was no concentration-QTc relationship for the drug (eravacycline) or its major metabolites (TP-498, TP-6208). The worst case scenario was unknown at the time of the review.

Reviewer's comments:

- *From the information in the current label, the worst case scenario seems to be severe hepatic impairment* (b) (4)

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

DHANANJAY D MARATHE
06/19/2018

CHRISTINE E GARNETT
06/19/2018

MEMORANDUM

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:	June 14, 2018
Requesting Office or Division:	The Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 211109
Product Name and Strength:	Xerava (eravacycline) for injection; 50 mg/vial
Applicant/Sponsor Name:	Tetraphase Pharmaceuticals, Inc
FDA Received Date:	June 8, 2018
OSE RCM #:	2018-41-2
DMEPA Safety Evaluator:	Sevan Kolejian, PharmD, 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 Xerava (eravacycline) for injection; 50 mg per vial (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response a recommendation that we made during a previous label and labeling review.[a]

2 DISCUSSION AND CONCLUSION

We note that in addition to our previous recommendations, the Applicant revised the container label and carton labeling. Below is a summary of revisions and rationale (if applicable):

- Name change from (b) (4) to XERAVA
- "(eravacycline) for injection" increased font size for better readability and change in color to align with final XERAVA product logo colors.
- Replaced (b) (4) with "50 mg per vial" in the ribbon for clarity and consistency with the vial label.
- Replaced (b) (4) with "For Intravenous Infusion Only." per changes requested by FDA in labeling PMR/PMC discussion comments (letter dated May 25, 2018).
- Replaced (b) (4) with "1 Single-Dose Vial" for clarity and FDA request.
- Added "Not labeled for individual sale" to clarify that the drug product's smallest saleable unit is a carton containing 12 single vial cartons.
- Entered the actual linear NDC barcode in the placeholder.
- Included actual manufacturer's SAP code, removed (b) (4) and included manufacturer's label document barcode in the placeholders and rotated the "Lot/Exp" text orientation.

We reviewed these revisions and the Applicant's rational for the revisions and found the revised container label and carton labeling for Xerava (eravacycline) for injection; 50 mg per vial are acceptable from a medication error perspective.

We have no further recommendations at this time.

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

[a] Kolejian, S. Label and Labeling Packaging Memorandum for Eravacyline for injection (NDA 21109). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAY 24. RCM No.: 2018-41-1.

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/s/

SEVAN H KOLEJIAN
06/14/2018

OTTO L TOWNSEND
06/15/2018

MEMORANDUM

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 24, 2018
Requesting Office or Division:	The Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 211109
Product Name and Strength:	Xerava (eravacycline) for injection; 50 mg/vial
Applicant/Sponsor Name:	Tetraphase Pharmaceuticals, Inc
FDA Received Date:	February 14, 2018
OSE RCM #:	2018-41-1
DMEPA Safety Evaluator:	Sevan Kolejian, PharmD, MBA
DMEPA Team Leader:	Otto L. Townsend , PharmD

1 PURPOSE OF MEMORANDUM

This memorandum serves as an addendum to our previous review[a] in which we evaluated the proposed label and labeling for Xerava (eravacycline) for injection; 50 mg per vial.

The Division of Anti-Infective Products (DAIP) requested that we reassess the container label and carton labeling because the proposed container label states "For Intravenous Infusion only" while the proposed carton labeling states (b) (4)

2 CONCLUSION

We reevaluated the proposed container label and carton labeling for Xerava (eravacycline) for injection; 50 mg per vial and determined that for consistency, the carton labeling statement (b) (4) should be revised to read "For Intravenous Infusion only" statement.

3 RECOMMENDATIONS FOR TETRAPHASE PHARMACEUTICALS, INC.

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

A. Carton labeling

   For consistency with the container label, revise the statement (b) (4) to read "For Intravenous Infusion only".

[a] Kolejian, S. Label and Labeling Packaging Review for Eravacyline for injection (NDA 21109). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APR 13. RCM No.: 2018-41.

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/s/

SEVAN H KOLEJIAN
05/24/2018

OTTO L TOWNSEND
05/24/2018

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:	April 13, 2018
Requesting Office or Division:	The Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 211109
Product Name and Strength:	Eravacycline for injection; 50 mg/vial
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Tetraphase Pharmaceuticals, Inc
Submission Date:	December 28, 2017 and February 14, 2018
OSE RCM #:	2018-41
DMEPA Safety Evaluator:	Sevan Kolejian, PharmD, MBA
DMEPA Team Leader:	Otto L. Townsend , PharmD

1 PURPOSE OF REVIEW VS REASON FOR REVIEW

As part of the approval process for Eravacycline for injection; 50 mg per vial, the Division of Anti-Infective Products (DAIP) requested that we review the proposed packaging, label and labeling for areas 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 (N/A)
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

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

We found the proposed container label and carton labeling acceptable from a medication error perspective. Table 2 below includes the identified medication error issues with the submitted prescribing information, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Division of Anti-Infective Products

Prescribing Information			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
General Issues			
1.	Use of the proprietary name, (b) (4) that was found unacceptable.	The name found unacceptable should not be included in the prescribing information (PI).	When a proprietary name is found conditionally acceptable, it should be used throughout the label and labeling.

2.	(b) (4)	(b) (4) the container label and carton labeling have the package-type term “single dose”.	We defer to the Office of Pharmaceutical Quality (OPQ) to determine the appropriate packaged-type term for this product. (b) (4)
3.	Use of trailing zero for dosing statements in the Highlights and Dosage and Administration sections.	The use of trailing zeros has led to ten-fold overdoses.	Remove the trailing zeros from the dosing statements in the Highlights and Dosage and Administration sections (e.g. change 1.0 mg to 1 mg).
Full Prescribing Information			
1.	(b) (4)	Eravacycline for injection dosing is weight based. (b) (4)	(b) (4)

4 CONCLUSION

Our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Eravacycline for injection that Tetraphase Pharmaceuticals submitted on February 14, 2018.

Table 2. Relevant Product Information for	
Initial Approval Date	N/A
Active Ingredient	Eravacycline
Indication	Treatment of complicated intra-abdominal infections in patients 18 years of age and older.
Route of Administration	intravenous
Dosage Form	for injection
Strength	50 mg / vial
Dose and Frequency	1 mg/kg by intravenous infusion over approximately 60 minutes every 12 hours for 4 to 14 days total duration.
How Supplied	Packaged as single vial carton and twelve vials carton containing 10 vials.
Storage	Stored at 2° to 8°C (36° to 46°F).
Container Closure	10 mL clear glass vials

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Eravacycline for injection labels and labeling submitted by Tetraphase Pharmaceuticals on March 26, 2018.

1. Container label
2. Carton labeling
3. Prescribing Information (Image not shown)

G.2 Label and Labeling Images

1. Container label: available on EDR at: \\cdsesub1\evsprod\nda211109\0006\m1\us\vial-label.pdf

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

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

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

/s/

SEVAN H KOLEJIAN
04/13/2018

OTTO L TOWNSEND
04/13/2018