CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211109Orig1s000

PRODUCT QUALITY REVIEW(S)

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
OFFICE OF NEW DRUGS
CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION

ADDENDUM #2 TO NDA #211109, DRUG PRODUCT REVIEW #1

DATE: July 30, 2018

SUBJECT: Acceptance of IR Amendment Responses and Final Drug Product approval recommendation for NDA 211109, XERAVA (Eravacycline) for Injection.

FDA Information Request

We are reviewing the Chemistry, Manufacturing, and Controls section(s) of your submission and have the following comments and information requests. We request a prompt written response by July 25, 2018 in order to continue our evaluation of your NDA.

With regards to section 11 of the PI and all relevant labeling for XERAVA, we acknowledge that the dihydrochloride is converted to the free base active moiety at pH adjustment of 5.5-7.0. The dihydrochloride is the active pharmaceutical ingredient and therefore a salt equivalency statement per USP Salt Policy is recommended in the label. We previously provided our recommendations to the PI.

Applicant Response

The changes recommended by FDA in *labeling PMR/PMC discussion comments* (letter dated May 25, 2018 [Reference ID 4268829]) and *information request* (letter dated July 23, 2018) related to a salt equivalency statement per USP Salt Policy were implemented in the updated proposed product prescribing information (PI). *Table 1* provides a summary of the changes performed in the updated PI document included with this submission.

The labeling was prepared to conform to the content and format regulations detailed in 21 CFR 201.56(a) and (d), and 21 CFR 201.57, including the Pregnancy and Lactation Labeling Rule. The following updated labeling documents are provided herein:

- *Package Insert* (MS Word)
- *Package Insert* (PDF)
- *Package Insert—track changes* (PDF)
- *Package Insert* (SPL)
  NOTE: the SPL file has not been updated with these changes; an updated SPL file will be submitted once labeling negotiations are complete for the NDA.

Response Evaluation and Recommendation

The response is acceptable. There are no outstanding issues or labeling comments. Approval of this application is recommended from the Drug Product perspective. Please see Drug Product Review #1 for full review details.

Milton J. Sloan, Ph. D., Sr. Chemist, Branch III, Division I, Office of New Drug Product, Office of Product Quality

Balajee Shanmugam, Ph.D., Branch Chief, Branch III, Division I, Office of New Drug Product, Office of Product Quality

Milton Sloan

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Date: 7/30/2018 11:08:28AM
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Balajee Shanmugam

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Date: 7/30/2018 11:13:01AM
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Addendum #1 to Review #1 NDA 211109

Date: June 8, 2018

To: **NDA 211109**

Through: Balajee Shanmugam, Ph. D. , Branch Chief, Division 1, Branch III

From: Milton J. Sloan, Ph. D. , Sr. Chemistry Reviewer, Division 1, Branch III

Subject: (b) (4) Labeling Review Comments for Xerava® (eravacyline) for Injection

(b) (4)

The recommended CMC labeling review evaluation for this NDA is attached. There are no other outstanding issues. Minor labeling negotiations continue.

Memorandum Prepared by

Milton J. Sloan, Ph. D. Sr. Chemist Reviewer — Date

for Concurrence:

Balajee Shanmugam. , Branch Chief, Division 1, Branch III — Date

ATTACHMENT:

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ATTACHMENT

LABELING

R Regional Information

1.14 Labeling

Highlights of Prescribing Information

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

- For injection, (b) (4): 50 mg eravacycline in a single-dose (b) (4) vial for reconstitution and further dilution. (3)

FULL PRESCRIBING INFORMATION: CONTENTS

3 DOSAGE FORMS AND STRENGTHS

For injection, (b) (4) : (b) (4) is a yellow to orange sterile powder for reconstitution (b) (4) (b) (4)

(b) (4)

Reviewer's Assessment:

Please see recommendations in tracked changes.

(b) (4)

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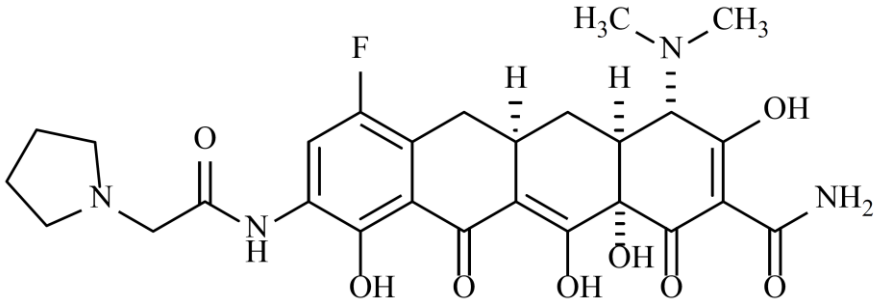
11 DESCRIPTION

XERAVA (eravacycline), , is a synthetic tetracycline class antibacterial agent for intravenous administration. Chemically, eravacycline is a C7-, C9-substituted sancycline derivative. (b) (4)

(b) (4) The chemical name of eravacycline is [(4*S*,4a*S*,5a*R*,12a*S*)-4-(dimethylamino)-7- fluoro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[2-(pyrrolidin-1-yl)acetamido]- 1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide]. The (b) (4) molecular formular for the dihydrochloride is $C_{27}H_{31}FN_4O_8 \cdot 2HCl$ Eravacycline molecular weight is (b) (4) .

The following represents the chemical structure of eravacycline:

(



(b) (4) XERAVA is a sterile, preservative-free lyophilized powder for intravenous (b) (4) after reconstitution and dilution. Each vial of XERAVA contains 50 mg of eravacycline (b) (4) (equivalent to (b) (4) mg of (b) (4) (b) (4) and 150 mg (b) (4) mannitol. Sodium hydroxide, and hydrochloric acid are used as needed for pH adjustment.

Reviewer's Assessment:

(b) (4)

Therefore, a salt equivalency statement is needed and was indicated to the Sponsor. The current guidance for industry "Naming of Drug Products Containing Salt Drug Substances" and the USP monograph <1121> is applicable because of current CDER policy. The name and strength is expressed based on the *formulated* drug substance and not how it may exist in the drug product. The guidance recommends an equivalency statement on the label to indicate the amount of active moiety related to the amount of active ingredient (salt).

The above sections in the Package Insert are acceptable with the recommended edits. Minor changes may be made on the PI Word document itself at the designated OND labeling meetings with the review team.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

XERAVA (b) (4) for injection, (b) (4) is (b) (4) a yellow to orange sterile, preservative-free, powder for reconstitution in single-dose 10-mL clear glass vials with a rubber stopper and an aluminum overseal. (b) (4) is supplied in two packaging configurations:

Single-dose vial carton containing one 50 mg per vial : NDC 71773-050-05

Twelve-vial carton containing twelve 50 mg per single-dose vial cartons: NDC 71773-050-12.

16.2 Storage

Prior to reconstitution, XERAVA should be stored at 2°C to 8°C (36°F to 46°F) *[see Dosage and Administration* (b) (4) *]*.

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

Distributed by:
Tetraphase Pharmaceuticals, Inc.
480 Arsenal Way, Ste 110
Watertown, MA 02472

(b) (4)™ is a trademark of Tetraphase Pharmaceuticals, Inc.
(b) (4) Tetraphase Pharmaceuticals, Inc. All rights reserved.
(b) (4)

Immediate Container Label

(b) (4)

(b) (4)

Reviewer's Assessment:

The use of the term "single-dose" container is not meant to imply the entire contents of the container constitute a single dose. The single-dose container contains more drug than is required for a single dose due to the required overfill in vials. The excess amount constituting more than one dose in the container should be discarded. Hence the statement "Discard Unused portion" is added. Reference is made to recent FDA's guidance for industry on *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products*. Furthermore, when dosed over an extended time period, the infusion containers (small volume) is considered single-dose containers because they are designed for use with a single patient as a single infusion. This is consistent with the Reviewer tool document for labeling.

{copy/paste or refer to a representative example of the proposed carton label here}

(b) (4)

Reviewer's Assessment:

The carton label complies with all regulatory requirements from a CMC perspective.

List of Deficiencies: None.

Primary Labeling Reviewer Name and Date:

Milton. J. Sloan, PhD,
Sr. Chemistry Reviewer
OPQ/ONDP/Div1/Branch III
6/8/2018Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Balajee Shanmugam, PhD
Branch Chief
OPQ/ONDP/Div1/Branch III

Milton Sloan

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Balajee Shanmugam

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Recommendation: ***Approval***

NDA 211109
Review # 1

Drug Name/Dosage Form	XERAVA™ (eravacycline) for Injection
Strength	50 mg/vial
Route of Administration	Intravenous infusion
Rx/OTC Dispensed	Rx
Applicant	Tetraphase Pharmaceuticals, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	December 28, 2017	All
Amendment (eCTD 012)	March 23, 2018	Microbiology
Amendment (eCTD 014)	April 16, 2018	Microbiology
Amendment (eCTD 015)	April 17, 2018	Drug Substance, Microbiology
Amendment (eCTD 017)	April 25, 2018	Facilities, Drug Product (b) (4)
Amendment (eCTD 019)	May 23, 2018	Drug Product

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Sithamalli Chandramouli	Charles Jewell
Drug Product	Milton Sloan	Balajee Shanmugam
Process	Jiao Yang	Upinder Atwal
Microbiology	Jason God	Denise Miller
Facilities	Jiao Yang	Derek Smith
Biopharmaceutics	Zhuojun Zhao	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)	N/A*		
	Type III			N/A*		
	Type III			Adequate	4/11/2017	
	Type III			N/A*		

**Sufficient information for the container closure systems was submitted in the NDA*

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	104839	IV formulation of eravacycline
IND		(b) (4)

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	Complete	Acceptable (*refer to DS and DP reviews*)		
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, eravacycline for 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 and an overall "Approve" recommendation was entered into Panorama by the Office of Process and Facilities (OPF) on April 18, 2018. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

II. Summary of Quality Assessments

A. Product Overview

Eravacycline is a synthetic, broad-spectrum fluorocyclic antibiotic belonging to the tetracycline class developed for the treatment of complicated intra abdominal infection (cIAI) caused by susceptible (b) (4) The proposed drug product, Xerava (eravacycline) for Injection, 50 mg, is a sterile lyophilized powder that needs to be reconstituted and further diluted for intravenous infusion.

Proposed Indication(s) including Intended Patient Population	Complicated intra abdominal infections (cIAI) in patients 18 years and older.
Duration of Treatment	The recommended dose regimen is 1 mg/kg every 12 hours. Intravenous infusions of XERAVA should be administered over approximately 60 minutes every 12 hours. The recommended duration of treatment with XERAVA for cIAI is 4 to 14 days. The duration of therapy should be guided by the severity and location of infection and the patient's clinical response.
Maximum Daily Dose	As above (*see the package insert for details*)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

(b) (4)

The drug product, eravacycline for injection, 50 mg, is a lyophilized powder for intravenous administration following reconstitution and dilution with appropriate diluents. Eravacycline for injection is supplied in a clear glass USP (b) (4) vial sealed with a grey (b) (4) stopper and an aluminum cap with a white flip-off seal. The excipients used in the drug product formulation include mannitol (b) (4) sodium hydroxide and hydrochloric acid as pH adjusters (b) (4) All excipients comply with the compendial standards. An overfill is used to allow for withdrawal of the labeled amount (50 mg) of eravacycline; (b) (4) Per instructions included in the package insert, the content of the vial is to be reconstituted with 5 mL of water for injection to deliver 10 mg/mL solution of eravacycline. This solution is to be further diluted to a target concentration of 0.3 mg/mL solution for intravenous infusion. The acceptable in-use chemical stability data were provided to support the storage time and conditions of the infusion (b) (4) using (b) (4) 0.9% Sodium Chloride Injection (b) (4) the (b) (4) package insert will recommend using only 0.9% Sodium Chloride Injection as a diluent for the preparation of eravacycline infusion solutions.

The drug product specification includes tests for appearance, visible particles, identification, assay, impurities, content uniformity, (b) (4) pH of reconstituted solution, particulate matter, endotoxins and sterility. The proposed specification (tests, acceptance criteria and analytical procedures, including (b) (4) HPLC for assay and impurities) was found acceptable. Information submitted in the NDA for the container closure system, including the results of extractable/leachable studies, was found acceptable to demonstrate its safety and suitability for intended use. The drug product stability information submitted in the NDA includes acceptable 18-month long-term and

6-month accelerated stability data for three full commercial scale batches manufactured at the proposed commercial manufacturing site, which support the proposed in the NDA expiration dating of 24 month for a drug product to be stored under refrigerated conditions of 5°C ± 3°C (b) (4). The overall information submitted in the NDA for the drug product was found acceptable by the Drug Product Reviewer.

The product quality microbiology review focused on the overall sterility assurance information submitted in the NDA for the proposed drug product that included issues such as container closure integrity (b) (4) packaging components, (b) (4) proposed microbiological controls for the drug product, etc. During the NDA review, additional information was requested regarding the container closure integrity testing, stopper (b) (4) validation, media fills, and endotoxin and sterility testing. These comments were adequately addressed by the Applicant, and the overall product quality microbiology information provided in the NDA and subsequent amendments was found acceptable by the Microbiology Reviewer.

Since the proposed dosage form is a lyophilized powder for solution to be administered via intravenous infusion, there is no need for dissolution testing. In addition, the proposed commercial drug product has the same formulation as the drug product used in the Phase 3 clinical trials; therefore, there is no need for bridging between different formulations. No biowaiver is requested nor required. Therefore, a Biopharmaceutics review was not needed for this NDA.

The Applicant has requested a categorical exclusion of the requirements of an environmental assessment (EA) under 21 CFR 25.31(b) based on the estimated concentrations of the substances at the point of entry into the aquatic environment (to be below 1 part per billion). The Applicant also stated in the NDA that no extraordinary circumstances exist that might cause this action to have a significant effect on the quality of the human environment. Therefore, the claim for an exclusion from an EA has been

found acceptable (as indicated in the Drug Product Chapter). The proposed package insert and container and carton labels are currently under assessment by the NDA review team and the labeling issues related to product quality will be addressed in a review addendum.

The eravacycline dihydrochloride drug substance is manufactured by (b) (4) In addition, several other facilities are involved in the drug substance testing. The manufacture of the drug product will be conducted at the (b) (4) Following a completion of the review of all facilities associated with the NDA, no outstanding issues that would prevent approval of this NDA were identified by the Facilities Reviewer. Therefore, the overall recommendation of "Approve" was entered for this NDA into Panorama by OPF on April 18, 2018.

(b) (4)

Based on the above assessments, this NDA is recommended for approval by the OPQ Review Team.

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

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

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MICROBIOLOGY

Product Background: The drug product is (b) (4) indicated for the treatment of complicated intra-abdominal infections in adults.

NDA: 211109

Drug Product Name / Strength: Eravacycline for injection / 50 mg

Route of Administration: IV

Applicant Name: Tetraphase Pharmaceuticals, Inc.

Manufacturing Site:
(b) (4)

Method of Sterilization: (b) (4)

Review Recommendation: Adequate.

Review Summary: (b) (4)
(b) (4)

List Submissions Being Reviewed:
12/28/2017
4/16/2018
4/17/2018
4/25/2018

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: The first round of Microbiology deficiencies were issued as three separate IRs as follows:

An initial IR was issued by the Agency on 23 February 2018. The applicant's response, received 16 April 2018, is addressed in the appropriate section of this review.

A second IR was issued by the Agency on 5 April 2018. The applicant's responses, received 17 April 2018, are addressed in the appropriate sections of this review.

The third IR was issued by the Agency on 19 April 2018. The applicant's response, received 25 April 2018 is addressed in the appropriate sections of this review.

Concise Description Outstanding Issues Remaining: (None)

Supporting Documents: (b) (4)

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

S Drug Substance

N/A. (b) (4)

P.1 Description of the Composition of the Drug Product

- **Description of drug product –**
  Lyophilized powder for injection.

- **Drug product composition –**

Table 1: Composition of Eravacycline

Component	Theoretical Quantity per Vial[2]	Function	Reference to Standard
Eravacycline[1]	50 mg	Active Pharmaceutical Ingredient	In-house
Mannitol	150 mg	(b) (4)	Ph. Eur., USP, JP
Sodium Hydroxide (NaOH)	As needed to adjust pH to target	pH adjustment	Ph. Eur., NF
Hydrochloric acid (HCl)	As needed to adjust pH to target	pH adjustment	Ph. Eur., NF
(b) (4)			Ph. Eur., USP
			Ph. Eur., USP

Table 1 was reproduced from Table 1 in "__cdsesub1_evsprod_nda211109_0001_m3_32-body-data_32p-drug-prod_eravacycline-injection_32p1-desc-comp_description-and-composition.pdf," located in Module 3.2.P.1

- **Description of container closure system –**

Table 2: Container closure components for Eravacycline

Container	Closure	Seal
10 mL (b) (4) (b) (4) USP (b) (4) glass, clear and colorless.	(b) (4)	20 mm Flip-off Seal, White cap

Table 2 was reproduced from Table 2 in "__cdsesub1_evsprod_nda211109_0001_m3_32-body-data_32p-drug-prod_eravacycline-injection_32p1-desc-comp_description-and-composition.pdf," located in Module 3.2.P.1

(b) (4)

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Denise Miller

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Jason God

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Date: 5/21/2018 12:12:53PM
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BIOPHARMACEUTICS

Product Background:

NDA: 211109 (505(b)(1))

Drug Product Name / Strength: (b) (4) **(eravacycline) powder for solution, 50 mg/vial**

Route of Administration: Intravenous infusion

Applicant Name: Tetraphase Pharmaceuticals, Inc.

Review Summary:

The proposed dosage form is a lyophilized powder for solution to be administered via intravenous infusion. Therefore, there is no need for dissolution testing.

The proposed commercial drug product has the same formulation as the drug product used in the Phase 3 clinical trials. Therefore, there is no need for bridging between different formulations.

No biowaiver is requested nor required.

The NDA for the proposed drug product does not require a Biopharmaceutics Review.

Primary Biopharmaceutics Reviewer Name and Date: Zhuojun Joan Zhao, Ph.D., 2/9/2018

Secondary Reviewer Name and Date: Elsbeth Chikhale, Ph.D., 2/14/2018

Zhuojun Zhao

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Date: 2/27/2018 03:54:46PM
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Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
Date: 2/27/2018 04:30:56PM
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ATTACHMENT I: Final Risk Assessments

From Initial Risk Identification			Review Assessment		
From Initial Risk Identification	**Review Assessment**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
		H, M, or L		Acceptable or Not Acceptable	
Assay /Stability	Formulation Raw materials Process parameters Scale/equipment Site	L	Sufficient evaluation of impurities/degradation products provided in the NDA Adequate acceptance criteria proposed	Acceptable	
Uniformity of Dose	Formulation Process parameters Scale/equipment Site	L	Adequate in-process controls implemented in the manufacturing process	Acceptable	
Reconstitution time	Formulation Raw materials Process parameters Scale/equipment Site	L	Data provided demonstrate adequate range	Acceptable	
Extractables and leachables	Formulation Container closure	L		Acceptable	*E/L studies should be performed with stopper change*
Endotoxins	Formulation Raw materials Process parameters Scale/equipment Site	M		Acceptable	
Sterility	Formulation Raw materials Process parameters Scale/equipment Site	H		Acceptable	

Particulate matter	Formulation Raw materials Process parameters Scale/equipment Site	M	Consistent data provided to demonstrate that the drug product meets <788>	Acceptable	

OVERALL RECOMMENDATION:
This NDA is recommended for Approval from the Product Quality perspective.
On behalf of OPQ Review Team
Dorota Matecka, ATL for NDA 211109

Dorota M.
Matecka -S