CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211109Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Application Type	NDA
Application Number	211109
PDUFA Goal Date	August 28, 2018
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Reviewer Name(s)	Mei-Yean Chen, Pharm.D.
Team Leader	Elizabeth Everhart, MSN, RN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	June 27, 2018
Subject	Evaluation of Need for a REMS
Established Name	Eravacycline
Trade Name	Xerava
Name of Applicant	Tetraphase Pharmaceuticals, Inc.
Therapeutic Class	Tetracycline class antimicrobial agent
Formulation(s)	50 mg vial
Dosing Regimen	1 mg/kg by intravenous infusion every 12 hours for 4-14 days.

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Xerava (eravacycline) is necessary to ensure the benefits outweigh its risks. Tetraphase Pharmaceuticals, Inc. (Tetraphase) submitted a New Drug Application (NDA) 211109 for eravacycline with the proposed indication for the treatment of complicated intra-abdominal infections (cIAIs) in patients 18 years of age and older. Eravacylcine is structurally similar to tetracycline-class antibiotics. The main serious risks associated with eravacycline are similar to the risks in the tetracycline class and include life-threatening hypersensitivity reactions, tooth discoloration and enamel hypoplasia, inhibition of bone growth, Clostridium difficile-associated diarrhea, potential for microbial overgrowth, tetracycline class adverse reactions, and development of drug resistant bacteria. These risks will be conveyed in the Warnings and Precautions section of the labeling.

The applicant did not submit a proposed REMS or risk management plan with this application.

DRISK and the Division of Anti-Infective Products (DAIP) agree that a REMS is not necessary to ensure the benefits of eravacycline outweigh its risks. A REMS has not been required for the tetracycline class of antibiotics. At the current time, there are no data showing that the risks of eravacycline are more concerning compared to other tetracycline antibiotics. The risks of eravacycline can be communicated in the labeling, as is the case for other tetracyclines.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Xerava (eravacycline) is necessary to ensure the benefits outweigh its risks. Tetraphase submitted a New Drug Application (NDA) 211109 for eravacycline with the proposed indication for the treatment of complicated intra-abdominal infections (cIAIs) in patients 18 years of age and older. This application is under review in DAIP. The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Xerava (Eravacycline), a new molecular entity (NME) [a], is a broad-spectrum fluorocycline antibiotic of the tetracycline class, proposed for the treatment of complicated intra-abdominal infections (cIAIs) in patients 18 years of age and older. Eravacycline exhibits an antibacterial activity profile similar to that of the carbapenems but covers Gram-positive pathogens more broadly. Eravacycline is being developed for the intravenous (IV) treatment of cIAI and complicated urinary tract infections due to its potential to treat serious hospital infections, particularly Gram-negative infections. Eravacylcine is supplied as 50 mg lyophilized powder for IV injection. The proposed regimen of eravacycline is 1 mg/kg IV every 12 hours

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

for 4-14 days[b]. Eravacycline was designated as a Qualified Infectious Disease Products (QIDP) and Fast Track with Priority review. Eravacycline is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for eravacycline NDA 211109 relevant to this review:

- July 9, 2013: Qualified Infections Disease Product (QIDP) designation granted
- March 27, 2014: Fast track designation granted
- December 28, 2017: NDA 211109 submission for the treatment of adult patients with complicated intra-abdominal infections (cIAI) received
- April 10, 2018: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for eravacycline. And an Advisory Committee meeting is not planned at this time.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Intra-abdominal infection (IAI) is a broad term that encompasses a number of infectious processes, including appendicitis, peritonitis, diverticulitis, cholecystitis, cholangitis, and pancreatitis. A common cause of IAI is appendicitis. According to DeFrances et al, each year >300,000 people develop appendicitis, resulting in over 1 million hospital days. [1] Furthermore, 30% of people are diagnosed with diverticulosis by age 60 years; 10% to 25% of these patients will eventually develop diverticulitis.[c] IAI is classified as uncomplicated or complicated based on the extent of the infection. Complicated intra-abdominal infection (cIAI) extends beyond the source organ into the peritoneal space and is associated with either abscess formation or peritonitis. Different bacterial pathogens are responsible for cIAI, including Gram-negative aerobic bacteria, Gram-positive bacteria, anaerobic bacteria, and mixed infection. When patients are diagnosed with cIAI, antibacterial drug therapy is recommended before, during, and after the planned surgical procedure.[2] cIAI is an important cause of morbidity and mortality and is the second most common cause of infectious mortality in the intensive care.[d]

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The management of cIAIs usually involves surgical and/or percutaneous drainage, removal of diseased tissue and adequate source control in conjunction with the use of braod-spectrum antibiotic or antibiotic combinations.[3] The major pathogens involved in community-acquired cIAIs are usual residents of the gastrointestinal (GI) tract. The microbiology of cIAIs is altered in patients who have been exposed to the healthcare setting. Healthcare-associated cIAIs are commonly caused by a more resistant flora, which may include Psudomonas aeruginosa and Acinetobacter spp., extended specrum beta-lactamase (ESBL)-producing Kelbsiella pneumoniae and Escherichia coli, carbapenemase-producing K. pneumoniae, enterococci, and Candida spp. Antibiotics used for the empiric treatment of cIAIs should have activity against enteric Gram-negative aerobic bacilli, enteric Gram-positive streptococci and enterococci. In addition, coverage for obligate anaerobic bacilli is recommended for distal small bowel, appendiceal, and colon-derived infections. Table 1[4] shows the available antibiotics to treat cIAI.

Table 1: Currently Available Treatments for cIAI by Antibacterial Class

Generic name	Trade name	Comments
Extended-spectrum penicillins		
Piperacillin	Pipracil	
Cephalosporins (parenteral 2nd, 3rd and 4th generation)		Use as empiric monotherapy has declined with emergence of multi-drug resistant gram-negative bacilli
Cefotetan	Cefotan	
Cefoxitin	Mefoxin	
Cefotaxime	Claforan	
Ceftazidime	Fortaz, Tazicef	
Ceftriaxone	Rocephin	
Cefepime	Maxipime	
β-lactam/β-lactamase Inhibitor Combinations		
Ticarcillin clavulanate	Timentin	
Ampicillin-sulbactam	Unasyn	
Piperacillin-tazobactam	Zosyn	
Ceftolozane-tazobactam	Zerbaxa	
Ceftazidime-avibactam	Avycaz	
Fluoroquinolones		Risk of tendonitis, tendon rupture, QTc prolongation, exacerbation of myasthenia gravis, CNS effects, peripheral neuropathy
Ciprofloxacin	Cipro	
Moxifloxacin	Avelox	
Carbapenems		
Imipenem-cilastatin	Primaxin	
Meropenem	Merrem	
Ertapenem	Envanz	
Doripenem	Doribax	
Monobactams		Addition of an agent against gram-positive cocci is recommended. Although used in pts with allergy to penicillins/cephalosporins, there are concerns about cross-reactivity with ceftazidime
Aztreonam	Azactam	
Aminoglycosides:		Nephrotoxicity & ototoxicity
Gentamicin, amikacin, tobramycin		
Glycylcyclines		Vancomycin-resistant *Enterococcus faecium*(VREF)

Tigecycline	Tygacil	activity, but *Pseudomonas aeruginosa* is intrinsically resistant to tigecycline
Other		
Clindamycin	Cleocin	Prevalence of resistance to *B. fragilis* group
Metronidazole	Flagyl	Recommended in combination for patients with
Linezolid	Zyvox	VREF Activity

4 Benefit Assessment

A total of 1,041 adults hospitalized with cIAI were randomized in 2 double-blind, active-controlled, multinational, multicenter trials (Trial 1, NCT01844856, and Trial 2, NCT02784704). These studies compared eravacylcine (1 mg/kg IV every 12 hours) with either ertapenem (1 gm every 24 hours) or meropenem (1 gm every 8 hours) as the comparator for 4-14 days. The primary efficacy endpoint was the clinical response at the Test of Cure (TOC) visit. Clinical cure was defined as complete resolution or significant improvement of signs or symptoms of the index infection at the TOC visit which occurred 25 to 31 days after randomization. The microbiologic intent-to treat (micro-ITT) population, which included all patients who had at least one baseline intra-abdominal pathogen, consisted of 846 patients in the 2 trials (see table 2). Per the clinical reviewer,[5] Table 2 showed strong evidence of non-inferiority (NI) within their respective NI margins of 10% and 12.5%[e], and secondary analyses (different timing of analysis visit and/or analysis population) were generally consistent with primary analysis findings.

Table 2: Clinical cure rates at TOC in the phase 3 trials, micro-ITT population

	Trial1		Trial 2	
Population	Eravacycline, n(%)	Ertapenem, n(%)	Eravacycline, n(%)	Meropenem, n (%)
	N=220	N=226	N=195	N=205
Clinical cure	191 (86.8)	198 (87.6)	177 (90.8)	187 (91.2)

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

5 Risk Assessment[6],[f]

Eravacycline was evaluated in 3 comparator-controlled clinical studies of adults with cIAI. AEs were evaluated for 576 patients treated with eravacycline and 547 patients treated with comparator drugs. Eravacycline was discontinued due to an AE in 9 of 576 (1.6%) patients and the comparator was discontinued due to an AE in 12 of 547 (2.2%) patients. The most frequently reported AEs (5% or greater) in patients receiving eravacycline and comparators were nausea and infusion site reation.

The serious risks associated with eravacycline are described in the sections below and will be communicated in the Warning and Precautions section of the label.

5.1 Hypersensitivity Reactions:

(b) (4)

Eravacycline is structurally similar to tetracycline class antibiotics and should be avoided in patients with known serious hypersensitivity to tetracycline class antibacterial drugs. Discontinue eravacycline if an allergic reaction occurs.

5.2 Tooth discoloration and enamel hypoplasia

The use of evaracycline during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-grey-brown). This adverse reactionis more common during long term use of the durgs of the tetracycline class, but it has been observed following repeated short term courses. Enamel hypoplasia has also been reported with drugs of the tetracycline class. Adivse the patient of potential risk to the fetus if eravacycline is used during the 2nd or 3rd trimester of pregnancy.

5.3 Inhibition of bone growth

Use of eravacycline during the 2nd and 3rd trimester of pregnancy, infancy and childhood up to the age of 8 years may cause reversible inhibition of bone growth. All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in premature infants given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued. Advise the patient of the potential risk to the fetus if eravacycline is used during the 2nd or 3rd trimester of pregnancy.

5.4 Clostridium difficile (C. diff.) Associated diarrhea

C. diff. associated diarrhea has been reported with use of nearly all antibacterial agents, and may range in severity from mild diarrhea to fatal colitis. C.diff. produces toxins A and B which contribute to the development of (b) (4). Hypertoxin producing strains of C. diff. cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy.

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the a drug.*

5.5 Potential for microbial overgrowth

Eravacycline use may result in overgrowth of non-susceptible organisms, including fungi. If such infections occur, discontinue eravacycline and institute appropriate therapy.

5.6 Tetracycline Class Adverse Reactions

Eravacycline is structurally similar to tetracycline class antibacterial durgs and may have similar adverse reactions (ARs). ARs including photosensitivity, peudotumor cerebri, and anti-anabolic action which has led to increased blood urea nitrogen, azotemia, acidosis, hyperphosphatemia, pancreatitis, and abnormal liver function tests, have been reported for other tetracycline class (b) (4), and may occur with eravacycline.

5.7 Development of Drug-Resistant Bacteria

Prescribing eravacycline in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug resistant bacteria.

6 Expected Postmarket Use

According to the current propsed indication, if approved, eravacycline will be used both in inpatient and outpatient (such as infusion centers or home infusion) settings.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for eravacycline beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of eravacycline on the basis of the efficacy and safety information currently available. Eravacylcine is structurally similar to tetracycline-class antibiotics. Life-threatening hypersensitivity reactions have been reported with other tetracycline antibiotics. This safety issue will be communicated in the labeling, in the section of contraindication and in the section of Warnings and Precautions. Other adverse events (AEs) including tooth discoloration and enamel hypoplasia, inhibition of bone growth, Clostridium difficile associated diarrhea, potential for microbial overgrowth, tetracycline class adverse reactions, and development of drug resistant bacteria will be conveyed in the Warnings and Precautions section of the labeling. A REMS has not been required for the tetracycline class of antibiotics. At the current time, there are no data showing that risks associated with eravacycline are more concerning than the other tetracyclines. These risks can be communicated in the labeling for eravacycline, as is the case for other tetracyclines.

9 Conclusion & Recommendations

DRISK and DAIP agree that the benefit-risk profile of eravacylcine is favorable, therefore, a REMS is not necessary to ensure its benefits outweigh its risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 REFERENCES

[1] DeFrances CJ, et al National Hospital Discharge Survey : 2005 annual summary with detailed diagnosis and procedure data. Vital Heal Stat. 2007; 165(13):1-209

[2] US Food and Drug Administration. Guidance for Industry. Complicated intra-abdominal infections: Developing drugs for treatment Published February 2015: www.fda.gov/downloads/drugs/guidance

[3] Solomkin, JS, JE Mazuski, JS Bradley et al., 2010, Diagnosis and Management of Complicated Intra-Abdominal Infection in Adults and Children: Guidelines by the Surgical Infection Society and the Infectious Disease Society of America, Clinical Infectious Diseases, 50:133-164.

[4] Eravacycline multidisciplinary review and evaluation, accessed June 14, 2018

[5] Needles, M, Mid-cycle presentation for eravacycline NDA 211109, April 10, 2018

[6] Proposed Prescribing Information for Eravacycline as currently edited by the FDA, last updated June 12, 2018.

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/s/

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