CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217417Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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 2, 2023
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 217417
Product Name, Dosage Form, and Strength:	Rezzayo (rezafungin) for Injection, 200 mg/vial
Applicant/Sponsor Name:	Cidara Therapeutics, Inc. (Cidara)
TTT ID #:	2022-608-1
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on February 28, 2023 for Rezzayo. The Division of Anti-Infectives (DAI) requested that we review the revised container label and carton labeling for Rezzayo (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

We note that the Applicant has implemented all of our container label recommendations, except "*…to add instructions for reconstituting the product (i.e. reconstitute with 9.5 mL of Sterile Water for Injection) and the resultant concentration (i.e., 20 mg/mL).*" We acknowledge that, as stated by the Applicant, "*…there is not adequate space on the container label to include the recommended instructions for reconstituting the product.*" Thus, based on the lack of space on the container label we find the Applicant's reasoning for not implementing our recommendation, to add instructions for reconstituting the product and the resultant concentration on the container label, acceptable from a medication error perspective. We have no additional recommendations at this time.

[a] Myers, D. Label and Labeling Review for Rezzayo (NDA 217417). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 OCT 07. TTT ID #: 2022-608.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON FEBRUARY 28, 2023

Container label

Carton labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DEBORAH E MYERS
03/02/2023 10:06:23 AM

VALERIE S VAUGHAN
03/02/2023 10:16:20 AM

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

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

Memorandum

Date: February 14, 2023

To: Eva Zuffova, Regulatory Project Manager
Division of Anti-Infectives (DAI)

From: Wendy Lubarsky, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for REZZAYO (rezafungin for injection), for intravenous use

NDA: 217417

Background:

In response to DAI's consult request dated December 23, 2022, OPDP has reviewed the proposed Prescribing Information (PI), and carton and container labeling for the original NDA submission for REZZAYO (rezafungin for injection), for intravenous use (Rezzayo).

PI:
OPDP's review of the proposed PI is based on the draft labeling accessed from Sharepoint on February 9, 2023, and we do not have any comments at this time.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on July 22, 2022, and emailed to OPDP on February 10, 2023. We concur with DMEPA's comments from October 27, 2022, and do not have any additional comments.

Thank you for your consult. If you have any questions, please contact Wendy Lubarsky at wendy.lubarsky@fda.hhs.gov .

21 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

WENDY R LUBARSKY
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Rare Diseases, Pediatrics,
Urologic and Reproductive Medicine
Division of Pediatrics and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

Division of Pediatrics and Maternal Health Review

Date:	February 2, 2023 **Date of Consult Request**: November 2, 2022
From:	Christos Mastroyannis, M.D., Medical Officer, Maternal Health Division of Pediatrics and Maternal Health (DPMH)
Through	Tamara Johnson, M.D., MS, Team Leader, Maternal Health, DPMH Lynne P. Yao, MD, Director, DPMH
To:	Division of Anti-Infectives (DAI)
NDA Number:	217417
Drug:	Rezzayo (rezafungin for injection) for intravenous use
Applicant:	Cidara Therapeutics, Inc
Indication:	Indicated for the treatment of candidemia and invasive candidiasis in adult patients
Subject:	Labeling review as per Pregnancy and Lactation Labeling Rule (PLLR).

Materials Reviewed

- Applicant's submission of July 22, 2022
- Division's Consult request of November 2, 2022, DARRTS Reference ID: 5071130
- Applicant's response to information request (IR) of December 2, 2022, received on January 10, 2023

INTRODUCTION

On July 22, 2022, the applicant, Cidara Therapeutics, Inc. submitted NDA 217417, for rezafungin, a New Chemical Entity (NCE), for the treatment of candidemia and invasive candidiasis in adult patients. This NDA was submitted under the 505(b)(1) pathway. Rezafungin was granted Orphan Drug Designation to treat invasive candidiasis in the US in February 2016, and in EU on June 1, 2021. The proposed labeling is in PLLR format. DAI has requested DPMH to ensure that the labeling complies with the PLLR content and format.

BACKGROUND

Candidemia and Invasive Candidiasis and Pregnancy

Candidemia refers to presence of Candida species in the blood. Candida in a blood culture should not be viewed as a contaminant and should prompt evaluation for metastatic infection.[1]

Invasive candidiasis refers to systemic Candida infection, in the presence or absence of candidemia; examples include osteoarticular infection and hepatosplenic candidiasis. Candidemia is the most common manifestation of invasive candidiasis.[2] Candidemia and invasive candidiasis in the general population does not differ from the disease course during pregnancy. Invasive candidiasis has estimated mortality rates of up to 47%.[3]

Patients at highest risk for development of candidemia include those receiving intensive care, including:

- Central venous catheters
- Total parenteral nutrition
- Broad-spectrum antibiotics
- Acute renal failure, particularly if requiring hemodialysis
- Prior surgery, particularly abdominal surgery
- Gastrointestinal tract perforations and anastomotic leaks
- Pancreatitis

and those who are immunocompromised including:

- Those with hematologic malignancies
- Recipients of solid organ or hematopoietic stem cell transplants
- Those given chemotherapeutic agents, especially those associated with extensive gastrointestinal mucosal damage

More females of reproductive potential are undergoing solid organ or hematopoietic stem cell transplants, predisposing them to **c**andidemia and invasive candidiasis.

In some areas of the United States, increasing rates of candidemia have been observed[2] in IV substance users.

Echinocandins belong to the five classes of antifungals available for the treatment of invasive candidiasis besides the azoles, polyenes, flucytosine and allylamine. They are the first line of treatment for candidemia and invasive candidiasis. There are insufficient human data with echinocandins use during pregnancy to determine a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animals, the drugs have been shown to cross the placenta and be present in fetal plasma, as well as being secreted in animal milk.[4]

Although it is nephrotoxic, amphotericin B is considered to be the safest systemic antifungal agent

[1] Fridkin SK. The changing face of fungal infections in health care settings. Clin Infect Dis 2005; 41:1455.

[2] Up to date: Candidemia in adults: Epidemiology, microbiology, and pathogenesis. Accessed November 30, 2022

3 Pilmis B, Jullien V, Sobel J, et al. Antifungal drugs during pregnancy: an updated review. J Antimicrob Chemother. 2015;70(1):14-22.

[4] Labelings for echinocandins

for use in pregnancy.[3] The liposomal formulation has a favorable risk/benefit profile, but other lipid formulations have not been adequately studied. The Infectious Diseases Society of America recommends systemic amphotericin B as the treatment of choice for invasive Candida infections in pregnant women.[3]

FDA has approved 3 drugs in the echinocandin class: caspofungin (NDA 021227 in 1/2001, micafungin (Mycamine NDA 021506 in 3/2005 and micafungin sodium NDA 212156 in 6/2021), and anidulafungin (NDA 021632 in 2/2006). All four labelings have been converted to PLLR in 2019, 2019 and 2021, and 2017 respectively. DPMH has not participated to these PLLR conversions.

Common adverse reactions with use of echinocandins include diarrhea, vomiting, nausea, pyrexia and anemia.

Drug Characteristics[5]

Half Life	(b) (4)
Molecular Weight	1285.46 Daltons
Protein bound	(b) (4) %
	(b) (4)
Administration	IV
Drug Class /antifungals	Echinocandins
Dosage:	400 mg loading dose followed by 200 mg weekly infusions over an hour.
Treatment duration:	(b) (4) .

Mechanism of action: Rezafungin is a semi-synthetic echinocandin. Rezafungin inhibits 1,3-β-D-glucan synthase enzyme complex, which is present in fungal cell walls but not in mammalian cells. This results in inhibition of the formation of 1,3-β-D-glucan, an essential component of the fungal cell wall of many fungi, including Candida species (spp.). Inhibition of 1,3-β-D-glucan synthesis results in concentration-dependent fungicidal activity against Candida spp.

REVIEW

Pregnancy

Non-clinical Data

In an embryofetal development study, intravenous rezafungin was administered to female rats one week prior to pairing with untreated males, and dosing was continued through mating to gestation day 17. Increased fetal incidence of retroesophageal aortic arch was observed in rat pups at 45 mg/kg, equivalent to 5 times the clinical exposure based on AUC comparisons.
In a pre- and post-natal development study in rats, at rezafungin doses up to 45 mg/kg, at 5 times the clinical exposure, based on AUC comparisons, there were no adverse effects on offspring

[5] Rezzyo applicant's proposed labeling of July 22, 2022 and edited by non clinical pharmacology

growth, maturation, or measures of neurobehavioral or reproductive function. No adverse outcomes were observed when rezafungin was dosed to pregnant rabbits during gestation up to 35 mg/kg, about 3 times the clinical exposure. The above findings were in agreement with the non clinical reviewer Owen G McMaster, Ph.D.

Findings from Animal Reproduction Studies as reported in the Labeling for Other Echinocandins

In animal reproduction studies of other echinocandins:

- **Caspofungin** caused embryofetal toxicity, including increased resorptions, increased peri-implantation loss, and incomplete ossification at multiple fetal sites when administered intravenously to pregnant rats and rabbits during organogenesis at doses up to 0.8 and 2 times the clinical dose, respectively
- **Micafungin** intravenous administration to pregnant rabbits during organogenesis at doses four times the maximum recommended human dose resulted in visceral abnormalities and increased abortions.
- **Anidulafungin** administered in mice with doses twofold higher than human exposures resulted in skeletal changes in rat fetuses and increased abortion and visceral abnormalities in rabbits.

Based on these animal findings, the respective labelings state that "The drug may cause fetal harm. Advise pregnant women of the risk to the fetus".

Clinical Data

As per applicant, pregnant and fertile females without birth control were excluded from clinical studies. As per applicant's pharmacovigilance report, there were no pregnancies during the drug development program.

Human Findings as reported in the Labeling for Other Echinocandins

- **Caspofungin:** There are insufficient human data to establish whether there is a drug-associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes with Caspofungin acetate for Injection use in pregnant women.
- **Micafungin:** There is insufficient human data on the use of micafungin for injection in pregnant women to inform a drug-associated risk of adverse developmental outcomes.
- **Anidulafungin:** There are no available human data on the use of ERAXIS in pregnant women to inform a drug-associated risk of adverse developmental outcomes.

Applicant's Review of Literature

The peer-reviewed publications included in the applicant's review of literature fall under three types: reviews (systematic literature reviews and meta-analysis), case-reports, and editorial letters. To identify all relevant publications, PubMed from MedLine bibliographic database was searched using the search terms (below) and strategies including combinations of Medical Subject Headings (MeSH). Terms included rezafungin, Rezzayo[6], echinocandin AND pregnanc*, pregnant women, gestation, gestational, first trimester, second trimester, third trimester, multiparous women, nulliparous women, placenta, and fetus*. Additional systematic literature reviews and meta-analysis were conducted in Cochrane Library database.

[6] Rezzayo has not been approved in US or EU. (b) (4)

Forty-nine publications were identified, of which 42 were dropped because other language than English, content not related to the review topic (e.g., focused on general pharmacology without considerations on pregnancy/lactation/fertility or off-label uses of echinocandins other than in pregnant/breastfeeding women, prevalence of Candida), different study population (e.g., preterm infants, critically ill or immunocompromised infants), provided ex-vivo, or in vitro susceptibility data.
No publications were identified with use of rezafungin in pregnancy. All seven publications referenced other echinocandins and they showed no evident safety issues in humans.
The applicant concludes that literature review on echinocandins use in pregnant women is limited.

DPMH Review of Literature
DPMH searched PubMed, Reprotox and GG Briggs and RK Freeman in Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk for use of rezafungin during pregnancy**.** No entries were identified. No additional studies have been identified in PubMed.

There are no nationwide data or dedicated pregnancy registries identified during the search by the applicant which could have contributed to a joint collection of data.

Summary
There are no data with rezafungin use in pregnant women to determine a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes.
In an embryofetal development study, intravenous rezafungin was administered to female rats one week prior to pairing with untreated males, and dosing was continued through mating to gestation day 17. Increased fetal incidence of retroesophageal aortic arch was observed in rat pups at dose exposures equivalent to 5 times the clinical exposure based on AUC comparisons. No adverse outcomes were observed when rezafungin was dosed to pregnant rabbits during gestation up to 35 mg/kg, about 3 times the clinical exposure.
In a pre- and post-natal development study in rats, at rezafungin doses up to 45 mg/kg, there were no adverse effects on offspring growth, maturation, or measures of neurobehavioral or reproductive function

Lactation
Non Clinical Data
Rezafungin was present in rat milk at low levels.

Clinical Review of Data
It is unknown whether rezafungin is present in human milk. As per applicant, there were no clinical studies involving lactating females.

Findings as reported in the Labeling for Other Echinocandins
The labelings for all 3 approved echinocandins (caspofungin, micafungin. and anidulafungin) are similar, stating: "There are no data on the presence of TRADENAME in human milk, the effects on the breast-fed infant or the effects on milk production". All were present in the milk of lactating rats following intravenous administration. When a drug is present in animal milk, it is likely that the drug will be present in human milk. All 3 approved echinocandin labelings carry the risk/benefit statement, "The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME , and any potential adverse effects on the breastfed child from TRADENAME, or from the underlying maternal condition."

Applicant's Review of Literature
To identify all relevant publications, the applicant searched PubMed from MedLine bibliographic database

using the search terms (below) and strategies including combinations of Medical Subject Headings (MeSH). Terms included rezafungin, Rezzayo, echinocandin AND breast feeding, breastfeeding, lactating, milk secretion OR colostrum. No publications were identified using rezafungin during lactation. There was only one publication by Njoku which refers to existing echinocandins in general.

- Njoku and colleagues (2010)[7] reviewed recent literature regarding the safety of antifungal agents in pregnant and breastfeeding patients and highlighted that echinocandins significantly expanded the treatment options available for invasive fungal infections. However, data on their use in pregnant and breastfeeding women were lacking.
- LactMed reviewing other echinocandins concludes that because they are highly bound to plasma proteins, over 95%, and because of poor oral bioavailability, it is unlikely to reach the milk and be absorbed by the infant. Echinocandins can safely be given intravenously to infants of aged 3 months or older. Any amount absorbed from milk is likely to be far less than an infant dose. If echinocandins are required by the mother, it is not a reason to discontinue breastfeeding.

DPMH Review of the Literature

Review by this reviewer of PubMed Reprotox/Micromedex, GG Briggs & RF Freeman in Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk and Halesmeds.com identified no entries.

Summary

There are no human data on the presence of rezafungin in human milk, the effects on the breastfed infant, or the effects on milk production. Rezafungin is present in animal milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because rezafungin is highly bound to plasma proteins, over 95%, and because of poor oral bioavailability, it is unlikely to reach the milk and be absorbed by the infant. Also, echinocandins can safely be given intravenously to infants of aged 3 months or older. There are no data in infants less than 3 months of age. No serious adverse reactions associated with the drug have been reported, therefore, there are no potential safety concerns for the breastfed infant and to advise mother not to breastfeed.

Females and Males of Reproductive Potential

Non-Clinical Data

Rezafungin did not affect mating or fertility in male and female rats following IV administration at doses equivalent up to 5 times the clinical exposure based on AUC comparisons. Decreased sperm motility was noted. Most males had no detectable motile sperm at doses equivalent to ≥ 5 times the clinical exposure based on AUC comparisons. Rezafungin was not genotoxic in a standard battery of assays, including an in vitro bacterial reverse mutation assay, an in vitro mammalian clastogenicity assay, and an in vivo rat bone marrow micronucleus assay.

Clinical Data

The applicant states that no published studies regarding the effects of echinocandins on human fertility were found and no studies were performed with rezafungin.

This reviewer did not identify any human data on the effects of rezafungin (or other echinocandin antifungal drugs) on fertility to inform a potential clinical risk. The applicant states (b) (4)

[redacted]

Findings as reported in the Labeling for Other Echinocandins

[7] Njoku J, Gumeel D, Hermsen E. Antifungal Therapy in Pregnancy and Breastfeeding. Curr Fungal Infect Rep (2010) 4:62-69

Nothing is stated in the labelings of the 3 approved echinocandins (caspofungin, micafungin and anidulafungin) about their use in "Females and Males of Reproductive Potential".

Summary

No relevant published information was identified by either the applicant or this reviewer for rezafungin use in patients of reproductive potential. Therefore, because rezafungin is not genotoxic or teratogenic, and does not have any reported effects on fertility, there is no need for pregnancy testing or contraception recommendations in labeling and subsection 8.3 Females and Males of Reproductive Potential will be omitted.

CONCLUSION

Rezafungin is not teratogenic or genotoxic. In an embryofetal development study in rabbits, no adverse outcomes were observed when rezafungin was dosed to pregnant rabbits during the period of organogenesis up to approximately 3 times the clinical exposure. Increased fetal incidence of retroesophageal aortic arch was observed in a rat embryofetal development study when rezafungin was administered to pregnant rats at 5 times the clinical exposure, based on AUC comparisons, during the period of organogenesis. There are no human data with rezafungin use during pregnancy to determine a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Treatment should not be withheld from pregnant patients who require a lifesaving medication.

For lactation, there are no studies and, therefore, no data to inform any safety concerns regarding rezafungin exposure. There are no data on fertility effects of rezafungin in patients of reproductive potential.

DPMH does not recommend a Post Marketing Requirement (PMR) for a descriptive pregnancy safety study or a lactation milk only study to collect safety data because such studies will be difficult to conduct in this patient population. The information collected will be highly confounded with other medications used in the critical care setting. It is also unlikely that these critical care patients will breastfeed their infants while being treated. (b) (4)

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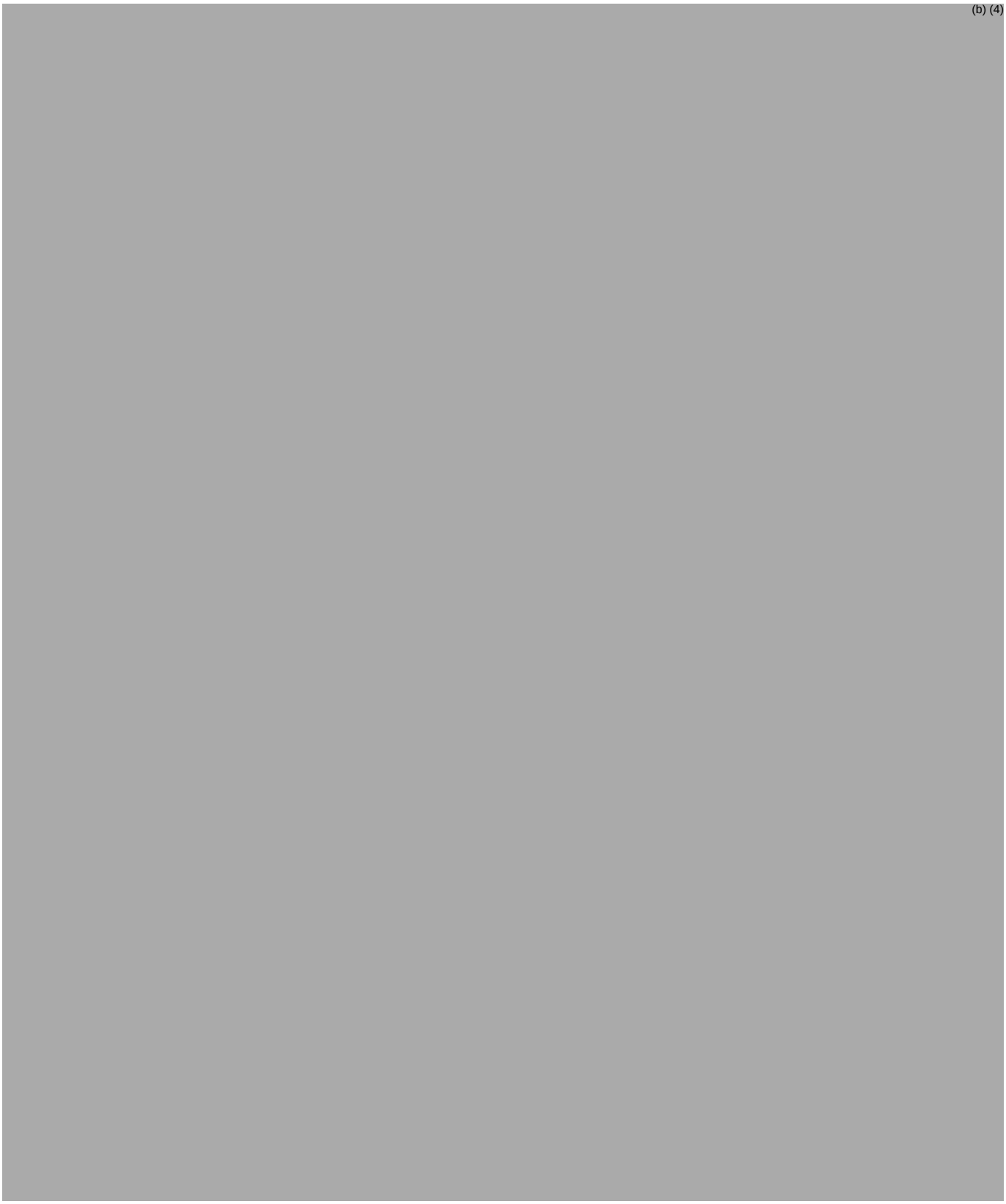
DPMH LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of rezafungin labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

(b) (4)




(b) (4)

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/s/

CHRISTOS MASTROYANNIS
02/02/2023 03:35:04 PM

TAMARA N JOHNSON
02/03/2023 10:19:27 AM

LYNNE P YAO
02/07/2023 12:43:05 PM

Clinical Inspection Summary

Date	December 14, 2022
From	Cheryl Grandinetti, Pharm.D. Clinical Pharmacologist Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Eva Zuffova, Regulatory Project Manager Shrimant Mishra, MD, Medical Officer Heidi Smith, MD, Medical Team Lead Peter Kim, MD, Division Director Division of Anti-infectives (DAI)
NDA #	217417
Applicant	Cidara Therapeutics, Inc
Drug	Rezafungin acetate for injection
NME	Yes
Proposed Indication	For the treatment of candidemia and/or invasive candidiasis
Consultation Request Date	August 22, 2022
Summary Goal Date	December 16, 2022
Action Goal Date	March 22, 2023
PDUFA Date	March 22, 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical investigators, Drs. Thompson, Vasquez, and Kotanidou, as well as the sponsor, Cidara Therapeutics, Inc., were inspected in support of NDA 217417 covering two clinical trials, Protocols CD101.IV.2.03 (The STRIVE Study) and CD101.IV.3.05 (The ReSTORE Study). Overall, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

During the clinical investigator inspections, the source records related overall response at Day 14 and all-cause mortality (ACM) at Day 30 in the STRIVE Study (i.e., primary and key secondary efficacy endpoints, respectively) and ACM at Day 30 and global cure at Day 14 in the ReSTORE Study (i.e., primary and key secondary efficacy endpoints, respectively) were reviewed and verified against the sponsor's data line listings in the 56 of the 75 randomized subjects at the 3 sites inspected. Source records reviewed included those documenting survival status at Day 30, investigator-reported systemic signs and symptoms of infection at Baseline and Day 14, fungal culture results from the local laboratory at all timepoints, and concomitant antifungal medications other than antifungals permitted in the protocols. No discrepancies were noted.

In addition, during the sponsor inspection, the central laboratory source records documenting

the fungal culture results at all timepoints were reviewed and verified against the sponsor's data line listings for the 75 randomized subjects in the two protocols at the 3 sites inspected. No issues or discrepancies were noted.

II. BACKGROUND

NDA 217417 was submitted to support the use of rezafungin acetate for injection for the treatment in adults with candidemia and invasive candidiasis. The pivotal studies supporting the application were the following:

- CD101.IV.2.03, "A Phase 2, Multicenter, Randomized, Double-blind Study of the Safety, Tolerability, and Efficacy of Intravenous CD101 vs Intravenous Caspofungin Followed by Oral Fluconazole Step-down in the Treatment of Subjects with Candidemia and/or Invasive Candidiasis (The STRIVE Study)"

- CD101.IV.3.05, "A Phase 3, Multicenter, Randomized, Double-blind Study of the Efficacy and Safety of Rezafungin for Injection versus Intravenous Caspofungin Followed by Optional Oral Fluconazole Step-down in the Treatment of Subjects with Candidemia and/or Invasive Candidiasis (The ReSTORE Study)"

Protocol CD101.IV.2.03 (The STRIVE Study) was a phase II, multicenter, prospective randomized, double-blind, two-part study of rezafungin for injection or intravenous (IV) caspofungin followed by oral fluconazole stepdown therapy for treatment of adult subjects with candidemia or invasive candidiasis. The primary objectives of this study were to evaluate the following:

- Safety and tolerability of rezafungin in the safety population
- Overall success (mycological eradication and resolution of systemic signs attributable to candidemia and/or invasive candidiasis) of rezafungin in subjects with candidemia and/or invasive candidiasis at Day 14 in the modified intent-to-treat (mITT) population

Subjects: A total of 207 subjects were enrolled in the study; for Part A, 115 subjects were screened, 107 were randomized and 73 completed the study; for Part B, 104 were screened, 100 were randomized and 75 completed the study.

Sites: The study was conducted at 68 study sites

Study initiation and completion dates: 26 Jul 2016 (first subject screened); 18 Apr 2019 (last subject visit)

Database Lock and Unblinding Dates:

- Part A interim DBL: 13 Nov 2017
- Part A interim DBL unblinding date: 14 Nov 2017 (unblinded to allow for unblinded interim evaluation of data from 70 subjects)

- Part A final DBL: 28 Feb 2018
- Part A final DBL unblinding date: 28 Feb 2018 (unblinded all 107 subjects in Part A)

The study duration was from 45 to 52 days for subjects with candidemia only or from 52-59 days for subjects with invasive candidiasis, with or without candidemia after the first dose of study drug as follows:

- Study drug administration from Day 1 up to Day 21 (for subjects with candidemia) or up to Day 28 (± 2 days; only for subjects with invasive candidiasis)
- Safety, tolerability, and efficacy assessments up to Day 21 (for subjects with candidemia) or up to Day 28 (± 2 days; only for subjects with invasive candidiasis)
- Follow up visit from Days 45 to 52 (for subjects with candidemia only) or Days 52-59 (for subjects with invasive candidiasis, with or without candidemia)

In Part A, eligible subjects were randomized in a 1:1:1 ratio to one of the following treatment groups:

- **Rezafungin Treatment Group 1:** Rezafungin IV 400 mg on Day 1 and Day 8 and an optional 400 mg dose on Day 15; and an optional 400 mg dose on Day 22. Oral stepdown therapy (matching placebo for fluconazole) allowed beginning on Day 4
- **Rezafungin Treatment Group 2:** Rezafungin IV 400 mg on Day 1, 200 mg on Day 8; an optional 200 mg dose on Day 15; and an optional 200 mg dose on Day 22 for subjects with invasive candidiasis. Oral stepdown therapy (matching placebo for fluconazole) allowed beginning on Day 4
- **Caspofungin Treatment Group 3:** Caspofungin IV 70 mg on Day 1, then 50 mg/day for 14 days; an optional 50 mg/day on Days 15-21; and an optional 50 mg/day on Days 22-28 for subjects with invasive candidiasis. Oral stepdown therapy (800 mg fluconazole) was allowed beginning on Day 4

Enrollment into Part A of the study closed and enrollment in Part B began after 107 subjects had been enrolled (i.e., 92 in the mITT population) in Part A. In Part B, 100 subjects were stratified (based on method used at Screening to establish diagnosis of candidemia or invasive candidiasis) and randomized in a 2:1 ratio to one of two Treatment Groups, rezafungin or caspofungin. Of note, under Protocol Amendment 5, subjects enrolled into Part B were randomized to Rezafungin Treatment Group 1 or the Caspofungin Treatment Group (See treatment regimen in Part A). After a complete review of unblinded Part A data, Amendment 6 defined Part B treatment and subjects subsequently enrolled under Amendment 6 were randomized to Rezafungin Treatment Group 2 or the Caspofungin Treatment Group (See treatment regimen in Part A). Subjects enrolled under Amendment 5 continued receiving their originally assigned study drug regardless of subsequent approval of Amendment 6.

In Parts A and B, all subjects received blinded treatment through Day 14. Optional additional treatment was available for all subjects on Day 15 (rezafungin groups) or Days 15-21 (caspofungin group). For the rezafungin treatment groups, matching placebo for caspofungin was given on other days (e.g., 16-21), if not stepped down. For subjects with invasive candidiasis, additional optional treatment was available on Day 22 (rezafungin groups) or Days

22-28 (caspofungin group). For the rezafungin treatment groups, matching placebo for caspofungin was given on other days (e.g., 23-28), if not stepped down. After ≥3 infusions, a switch to oral step-down treatment was available if the predefined criteria (as outlined in the protocol) were met.

Safety was assessed from Screening to the follow-up visit through the evaluation of AEs, vital signs (temperature, heart rate, blood pressure, and respiratory rate), ECGs, and clinical laboratory data (clinical chemistry panels, hematology evaluations, and urinalyses). Concomitant systemic antifungal agents, other than those listed as part of study drug therapy, were not permitted during the trial, and their use, for any reason other than the subject being considered a treatment failure, must have been discussed with the Medical Monitor before administration.

The ***primary efficacy outcome measure*** was overall response (i.e., success, failure, and indeterminate) at Day 14 (±1 day). Overall response was determined by the following:

- The mycological response
- Investigator assessment of systemic signs attributable to candidemia. Signs of candidemia/invasive candidiasis were fever, hypothermia, tachycardia, tachypnea, or hypotension. Resolution of signs of infection was determined programmatically.

Overall response of success was defined as mycological eradication/presumed eradication and resolution of attributable systemic signs of candidemia and/or invasive candidiasis that were present at baseline.

A key ***secondary efficacy endpoint*** was 30-day all-cause mortality (ACM). Subjects who did not die or were lost to follow-up were censored in the analysis at the last date known to be alive.

Efficacy assessment were performed on Day 5 and Day 14; on Day 28 for subjects with invasive candidiasis; and at the Follow-up visit (Days 45–52 for subjects with candidemia only or Days 52–59 for subjects with invasive candidiasis with or without candidemia). Blood cultures were performed daily or every other day until 2 blood cultures drawn ≥12 hours were negative without an intervening positive culture.

Protocol CD101.IV.3.05 (The ReSTORE Study) was a Phase 3, multicenter, prospective, randomized, double-blind, efficacy and safety study of rezafungin for injection (IV) versus a caspofungin IV followed by optional oral fluconazole stepdown therapy in subjects with candidemia and/or invasive candidiasis. The primary objectives of this study were to demonstrate that rezafungin for injection is noninferior to caspofungin for:

- ACM at Day 30 (-2 days) in subjects who had a documented *Candida* infection based on Central Laboratory evaluation of a culture from blood or another normally sterile site obtained ≤4 days (96 hours) before randomization and received ≥1 dose of study drug (i.e., the modified Intent-to-Treat (mITT) population)

- Global cure at Day 14 (±1 day) in the mITT Population (clinical cure as assessed by the Investigator, radiological cure [for qualifying invasive candidiasis subjects], and mycological eradication, as confirmed by the Data Review Committee [DRC])

Subjects: A total of 222 subjects were screened; 199 were randomized (i.e., 100 subjects were randomized to receive rezafungin and 99 subjects were randomized to receive caspofungin); 118 subjects completed the study; and 187 subjects were included in the mITT population

Sites: The study was conducted at 66 study sites

Study initiation and completion dates: 12 Oct 2018 (first subject screened); 7 Oct 2021 (last subject visit)

Database Lock Date: 30 Nov 2021

Study Unblinding: 01 Dec 2021

The study consisted of the following:

- A Screening Period (≤4 days, 96 hours)
- A Required Treatment Period (Day 1 to Day 14)
- An Optional Extended Treatment Period (Day 15 to Day 28)
- A Follow-up Period (Days 52 to 59)

Subjects were randomized to receive rezafungin or caspofungin in a 1:1 ratio. The study treatments were administered in the hospital in a blinded manner to maintain the integrity of the study blind as follows:

- **Rezafungin for injection Treatment Group:**
    - Rezafungin 400 mg, administered by IV infusion over 60 minutes (and could be increased up to 180 minutes to manage infusion-related reactions [IRR]) on Week 1, Day 1 followed by 200 mg on Day 8 with optional doses of 200 mg on Day 15 and Day 22, for a total of 2 to 4 doses.
    - Saline placebo to match for caspofungin IV, which was administered on Days 2–7, Days 9– 14, and during the optional dosing period on Days 16–21 and Days 23–28
    - Daily placebo to match fluconazole for oral stepdown therapy (first eligibility on Day 4 or later as advised by a site's national/regional/local guidelines), which was administered every day including on rezafungin IV infusion days.
- **Caspofungin IV Treatment Group:**
    - Caspofungin 70 mg IV loading dose on Day 1, followed by caspofungin 50 mg IV once daily for 14 days with the option to continue treatment for up to 28 days

- Oral fluconazole 6 mg/kg (to the nearest 200 mg) with a maximum dose of 800 mg administered once daily beginning on Day 4 for subjects who met the oral stepdown eligibility criteria
- Fluconazole was administered after ≥3 days (or the minimum duration of IV therapy advised by the site's national/regional/local guidelines, whichever was greater) of caspofungin treatment
- Matching IV saline placebo for rezafungin for injection once weekly on the days of scheduled rezafungin for injection doses until study drug was stopped (Day 8; Day 15 [if applicable] and Day 22 [if applicable])

Safety was assessed through the evaluation of AEs, vital signs (temperature, heart rate, blood pressure, and respiratory rate), physical examinations, ECGs, and clinical laboratory data (clinical chemistry panels, hematology evaluations, and urinalyses). Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) system version 5.0.

The primary efficacy outcome was ACM at Day 30 (-2 days) in the mITT analyses set.

The ***key secondary efficacy outcome*** was global cure at Day 14 (±1 day) in the mITT population. Global cure was based on the following:

- Clinical cure as assessed by the Investigator
- Radiological cure [for qualifying invasive candidiasis subjects]
- Mycological eradication confirmed by an independent DRC at Day

Efficacy assessments were conducted as follows:

- Survival status was assessed at Day 30 (-2 days) and the Follow-up visit (Days 52–59).
- Global response was assessed and determined on Day 5, Day 14 (±1 day), Day 30 (-2 days), EOT (≤2 days of last dose), and Follow-up (Days 52–59) and confirmed by the DRC.
- Blood cultures were repeated daily (preferred) or every other day until the first negative blood culture result for *Candida spp*. with no subsequent positive culture (in cases when one or more samples were drawn and cultured after the first negative culture was available).

Fungal Testing Performed in both studies, the ReSTORE and STRIVE Studies:

For both studies, the primary fungal isolate species identification and susceptibility testing was performed at the local site laboratory for *Candida* for blood or normally sterile tissue/fluid culture according to the local institution standard operating procedures. All fungal isolates cultured during screening and subsequent visits from blood or normally sterile tissue/fluid were shipped to a central laboratory per instructions specified in the central lab and/or biorepository manual for the designated geographic region (see Background Package for each study's central lab manuals). Central laboratory results were not provided to the clinical investigators during

and after the trial. The local lab microbiology report was used for subject qualification for the trial and to establish the best treatment plan per local standard of care.

Rationale for Site Selection

The clinical sites were selected based on enrollment, participation in the 2 clinical trials being inspected, and previous inspection history.

III. RESULTS (by site):

1. **George R. Thompson, MD**
   Site# 01004
   University of California-Davis Medical Center
   2315 Stockton Boulevard
   Sacramento, CA 95817
   PDUFA Inspection Dates: 5 to 17 October 2022

At this site for Protocol CD101.IV.2.03 (the STRIVE Study), 28 subjects were screened; 26 were randomized and 24 subjects completed the study. Per the applicant's data line listings, Subject (b) (6) (randomized to caspofungin) died on Day 10 (i.e., secondary to fungal peritonitis leading to respiratory and cardiac failure) and Subject (b) (6) (randomized to rezafungin Group 1) was lost to follow-up on Day 15. For Protocol CD 101.IV.3.05 (the ReSTORE Study), 21 subjects were screened, 19 subjects were randomized, and 16 subjects completed the study. Per the applicant's data line listings, Subject (b) (6) (randomized to rezafungin) discontinued treatment on Day 10 because of the inability to return to the study site to obtain additional study medication; Subject (b) (6) (randomized to rezafungin) was placed in hospice care on Day 41; and Subject (b) (6) (randomized to caspofungin) died on Day 56 (i.e., secondary to lipoid pneumonia leading to worsening respiratory failure).

A full audit of the study records for 13 of the 26 randomized subjects in the STIVE Study and 13 of the 19 randomized subjects in the ReSTORE Study was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; Institutional Review Board (IRB) submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records including those related to verification of the primary and key secondary efficacy endpoints of overall response at Day 14 and all-cause mortality (ACM) at Day 30, respectively in the STRIVE Study, and ACM at Day 30 and global cure at Day 14, respectively in the ReSTORE Study; adverse event reporting; protocol deviations; drug accountability logs and processes and procedures in place for blinding the study medication; monitor logs and follow-up letters; and other regulatory documentation (e.g., financial disclosures, Form FDA 1572).

There was no evidence of under-reporting of adverse events. The source records documenting the primary and key secondary efficacy endpoint data (i.e., survival status at Day 30,

investigator-reported systemic signs and symptoms of infection at Baseline and Day 14, fungal culture results from the local laboratory at all timepoints, and concomitant antifungal medications other than antifungals permitted in the protocol) were reviewed and verified against the sponsor's data line listings for 13 of the 26 randomized subjects in the STIVE Study and 13 of the 19 randomized subjects in the ReSTORE Study. In addition, source records documenting the radiological assessments were verified against the sponsor's data line listings in 13 of the 19 randomized subjects in the ReSTORE Study. No discrepancies or issues were noted.

2. Jose Vazquez, MD
Site# 01071
Augusta University
1120 15th Street AE-3029
Augusta, GA 30912
PDUFA Inspection Dates: 11 to 14 October 2022

At this site for Protocol CD101.IV.2.03 (the STRIVE Study), 8 subjects were screened, 8 were randomized, and 3 subjects completed the study. Per the applicant's data line listings, Subject (b) (6) (randomized to caspofungin) withdrew consent after randomization; Subjec (b) (6) (randomized to rezafungin Group 1) withdrew consent on Day 12 for unspecified reasons; Subject (b) (6) (randomized to rezafungin Group 2) withdrew consent on Day 1 for unspecified reasons; Subject (b) (6) (randomized to caspofungin) was withdrawn on Day 4 due to qualifying blood cultures that was negative; and Subject (b) (6) (randomized to rezafungin Group 1) was lost to follow-up on Day 29.

For Protocol CD 101.IV.3.05 (the ReSTORE Study), 10 subjects were screened, 10 were randomized, and 7 completed the study. Per the applicant's data line listings, Subject (b) (6) (randomized to rezafungin) withdrew consent on Day 7 due to subject being placed in hospice; Subjec (b) (6) (randomized to rezafungin) was withdrawn from the study on Day 1 due to an adverse event (i.e., infusion-related reaction); and Subject (b) (6) (randomized to caspofungin) was lost to follow-up on Day 8.

A full audit of the study records for the 8 randomized subjects in the STIVE Study and the 10 randomized subjects in the ReSTORE Study was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; IRB submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records including those related to verification of the primary and key secondary efficacy endpoints of overall response at Day 14 and all-cause mortality (ACM) at Day 30, respectively in the STRIVE Study and ACM at Day 30 and global cure at Day 14, respectively in the ReSTORE Study; adverse event reporting; protocol deviations; drug accountability logs and processes and procedures in place for blinding the study medication; monitor logs and follow-up letters; and other regulatory documentation (e.g., financial disclosures, Form FDA 1572).

There was no evidence of under-reporting of adverse events. The source records documenting

the primary and key secondary efficacy endpoint data (i.e., survival status at Day 30, investigator-reported systemic signs and symptoms of infection at Baseline and Day 14, fungal culture results from the local laboratory at all timepoints, and concomitant antifungal medications other than antifungals permitted in the protocol) were reviewed and verified against the sponsor's data line listings for the 8 randomized subjects in the STIVE Study and the 10 randomized subjects in the ReSTORE Study. In addition, source records documenting the radiological assessments were verified against the sponsor's data line listings in the 10 randomized subjects in the ReSTORE Study. No discrepancies or issues were noted.

3. Anastasia Kotanidou, MD
Site# 04031
General Hospital of Athens Evangelismos
45-47 Ypsilantou Str.
Athens PC 10676 Greece
PDUFA Inspection Dates: 31 October to 4 November 2022

At this site for Protocol CD101.IV.2.03 (the STRIVE Study), 8 subjects were screened, 6 were randomized and 3 subjects completed the study. Per the applicant's data line listings, Subject (b) (6) (randomized to rezafungin Group 1) died on Day 9 (i.e., secondary to multi-organ failure and septic shock); Subject (b) (6) (randomized to rezafungin Group 1) died on Day 16 (i.e., septic shock); and Subject (b) (6) (randomized to rezafungin Group 1) was lost to follow-up on Day 75. For Protocol CD 101.IV.3.05 (the ReSTORE Study), 6 subjects were screened, 6 were randomized, and 4 subjects completed the study. Per the applicant's data line listings, Subject (b) (6) (randomized to caspofungin) withdrew consent on Day 7 for unspecified reasons and Subject (b) (6) (randomized to caspofungin) was lost to follow-up on Day 33.

A full audit of the study records for 6 randomized subjects in the STIVE Study and 6 randomized subjects in the ReSTORE Study was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; Ethics Committee submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records including those related to verification of the primary and key secondary efficacy endpoints of overall response at Day 14 and all-cause mortality (ACM) at Day 30, respectively in the STRIVE Study and ACM at Day 30 and global cure at Day 14, respectively in the ReSTORE Study; adverse event reporting; protocol deviations; drug accountability logs and processes and procedures in place for blinding the study medication; monitor logs and follow-up letters; and other regulatory documentation (e.g., financial disclosures, Form FDA 1572).

There was no evidence of under-reporting of adverse events. The source records documenting the primary and key secondary efficacy endpoint data (i.e., survival status at Day 30, investigator-reported systemic signs and symptoms of infection at Baseline and Day 14, fungal culture results from the local laboratory at all timepoints, and concomitant antifungal medications other than antifungals permitted in the protocol) were reviewed and verified against the sponsor's data line listings for the 6 randomized subjects in the STIVE Study and

the 6 randomized subjects in the ReSTORE Study. In addition, source records documenting the radiological assessments were verified against the sponsor's data line listings in the 6 randomized subjects in the ReSTORE Study. No discrepancies or issues were noted.

4. Cidara Therapeutics, Inc.
6310 Nancy Ridge Dr., Suite 101
San Diego CA 92121
*PDUFA Inspection Dates:*8 to 16 Nov 2022

The inspection of Cidara Therapeutics, Inc. focused on and covered roles and responsibilities; the organization and its personnel; registration of studies on clinicaltrials.gov; Cidara's quality management system; oversight of the clinical trial conduct, monitoring procedures, and activities; drug accountability; adverse event reporting; process for managing protocol deviations; data collection, handling, and management, including use of service providers who handled and managed critical study data (e.g., central laboratory fungal culture result data); record retention; and financial disclosure. Records reviewed during the inspection included those related to investigator agreements, service provider agreements, and contracts; written standard operating procedures; handling and processing of protocol deviations; fungal culture testing results for Sites 01004, 01071, and 04031; adverse event reporting; drug accountability; relevant communication and correspondence; and monitoring activities.

The source records documenting the fungal culture results from the central laboratory at all timepoints were reviewed and verified against the sponsor's data line listings for the 40 randomized subjects in the STIVE Study and the 35 randomized subjects in the ReSTORE Study at Sites 01004, 01071, and 04031. The inspector was provided direct access to the central laboratory systems for data verification purposes. No issues or discrepancies were noted.

{See appended electronic signature page}

Cheryl Grandinetti, Pharm.D.
Clinical Pharmacologist
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Central Doc. Rm. NDA 217417
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DAI/Medical Team Leader/Heidi Smith
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OSI/DCCE/GCP Reviewer/Cheryl Grandinetti
OSI/GCP Program Analysts/Yolanda Patague

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHERYL A GRANDINETTI
12/15/2022 06:49:24 AM

PHILLIP D KRONSTEIN
12/15/2022 08:20:37 AM

JENN W SELLERS
12/15/2022 08:42:05 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	October 27, 2022
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 217417
Product Name and Strength:	Rezzayo (rezafungin) for Injection, 200 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Cidara Therapeutics, Inc. (Cidara)
FDA Received Date:	July 22, 2022
TTT ID #:	2022-608
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 REASON FOR REVIEW

As part of the approval process for Rezzayo (rezafungin) for Injection, the Division of Anti-Infectives (DAI) requested that we review the proposed Rezzayo prescribing information (PI), container label, and carton labeling for 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 – N/A
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Label and Labeling	F

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

3 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), container label, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Cidara Therapeutics, Inc.

4 RECOMMEDATIONS FOR DIVISION OF ANTI-INFECTIVES (DAI)

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
Highlights of Prescribing Information			
1.	As currently presented, preparation instructions	The instructions regarding reconstitution of (b) (4)	We acknowledge the space limitations of the Highlights of

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	are not included in the Highlights of Prescribing Information.	power and further preparation of the intravenous infusion solution are complex. Lack of understanding the appropriate directions for reconstitution of the (b) (4) powder and preparation of the intravenous infusion solution, could result in wrong technique in preparing the product, which could lead to wrong dose medication errors.	Prescribing Information; thus we recommend including a statement such as "See full prescribing information for reconstitution, dilution, and administration instructions. (2.x)" in the Highlights of Prescribing Information, under Dosage and Administration section, to alert the health care practitioner that additional critical information is in the Full Prescribing Information.
Full Prescribing Information – Section 2 *Dosage and Administration*			
1.	As currently presented, the text in subsection 2.2 *Administration Instructions*, includes (b) (4) However, this product is intended for intravenous infusion. Additionally, the proposed container label and carton labeling includes the route of administration statement "For Intravenous Infusion Only" on the principal display panels (PDP).	We are concerned that the drug could be inadvertently administered as an (b) (4) Additionally, inconsistent labeling statements across all elements of the labeling (e.g., container, carton, and prescribing information) may contribute to confusion that can result in medication error.	To provide clarification and consistent language regarding the intended route of administration, revise the text (b) (4) to "For Intravenous Infusion Only."
2.	As currently presented, subsection 2.3 under the header title "Storage of the Reconstituted Solution", the storage information is not presented in a	We are concerned that as currently presented that storage information could be misinterpreted and result in a deteriorated product medication error. Temperature ranges are	To provide clarity revise the current text (b) (4) such that the intended storage temperatures appear

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	standardized manner [redacted]	usually presented in a standardized format from the low to the high end of the temperature range. Additionally, per USP[a], the Centigrade temperature(s) precede the Fahrenheit temperature(s) in storage statements.	as a range in which the Centigrade temperature precedes the associated Fahrenheit temperature enclosed in parenthesis. For example, "…solution can be stored between 5°C to 25°C (41°F to 77°F)." and "…for 24 hours at 5°C to 25°C (41°F to 77°F)." Additionally, revised the statement [redacted] o "…when stored at 5°C to 25°C (41°F to 77°F)."
3.	As currently presented, the error prone [redacted] is included in the subsection 2.3 header titles [redacted] as well as throughout the text in subsection 2.3 and subsection 2.4, [redacted] as well as throughout the text in subsection 2.4.	[redacted] can be misinterpreted and result in wrong route medication errors.	Replace [redacted] with [redacted] "intravenous," throughout the titles and text of subsections 2.3 and 2.4.
4.	As currently presented, subsection 2.3 header title [redacted] the storage information is	See rational for concern listed above under Full Prescribing Information – Section 2 *Dosage and Administration*, line 2.	To provide clarity revise the current text [redacted]

[a] USP General Chapter <659> Packaging and Storage Requirements.

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	not presented in a standardized manner. (b) (4)		(b) (4) such that the intended storage temperatures appear as a range in which the Centigrade temperature precedes the associated Fahrenheit temperature enclosed in parenthesis. For example, "…solution can be stored between 5°C to 25°C (41°F to 77°F)." and "…for 48 hours at 5°C to 25°C (41°F to 77°F)." Additionally, revised the statement (b) (4) to "…when stored at 5°C to 25°C (41°F to 77°F)."
5.	As currently presented, subsection 2.4 includes the text (b) (4)	Post-marketing reports support (b) (4) can be overlooked and the warning may be misinterpreted as an affirmative action.[b]	To provide clarity we recommend (b) (4) in the sentence or completely deleting this (b) (4) statement. For example, (b) (4)
Full Prescribing Information – Section 3 *Dosage Forms and Strengths*			
1.	As currently presented, the dosage form (i.e., for Injection) is not included.	Per 21 CFR 201.57(c)(4) "This section must contain information on the available dosage forms to which the labeling applies…".	Include the dosage form (i.e., for Injection).

[b] Institute for Safe Medication Practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3.

5 RECOMMENDATIONS FOR CIDARA THERAPEUTICS, INC.

Table 3. Identified Issues and Recommendations for Cidara Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	The format for expiration date is not defined.	Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a forward slash be used to separate the portions of the expiration date.
Container Label			
1.	As currently presented, the package type term (i.e., “Single-Dose Vial”) is not included on the container label.	The contents of the vial could be inadvertently “saved” for future use and result in use of deteriorated drug product medication errors.	Add the appropriate package type term (i.e., “Single-Dose Vial”) to the container label. Additionally, we recommend that the package type term be followed by the statement “Discard Unused Portion.”

Table 3. Identified Issues and Recommendations for Cidara Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			For example: "Single-Dose Vial – Discard Unused Portion"
2.	As currently presented, the "Recommended Dosage" statement is not included on the container label.	21 CFR 201.55 requires "…labels for prescription drugs bear a statement of the recommended or usual dosage."	Add your intended "Recommended Dosage" statement. For example, "Recommended Dosage: See prescribing information."
3.	As currently presented, the principal display panel (PDP) does not include information regarding the need for reconstitution and further dilution of this product prior to administration.	Lack of understanding the need to reconstitute the (b) (4) powder and further dilute this product prior to intravenous administration, could result in product preparation medication errors.	Consider adding to the PDP information regarding the need for reconstitution and further dilution of this product prior to administration. For example, "Must be reconstituted and further diluted."
4.	As currently presented, instructions for reconstituting the product (i.e., reconstitute with 9.5 mL of Sterile Water for Injection) or the resultant concentration (i.e., 20 mg/mL) are not included. Additionally, information regarding the need for further dilution is not included.	To avoid medication errors involving wrong strength/concentration, instructions for reconstituting the product and the resultant concentration (i.e., 20 mg/mL) should be included on the container label (vial) if space permits. These instructions will inform persons responsible for preparing the product what type and volume of diluent should be used for reconstitution, and the amount of drug contained in each milliliter (mL) once reconstituted.	To decrease the potential for wrong dose medication errors, if space permits, add instructions for reconstituting the product (i.e., reconstitute with 9.5 mL of Sterile Water for Injection) and the resultant concentration (i.e., 20 mg/mL). For example: Add to the container label (vial) side panel "Reconstitute with 9.5 mL Sterile Water for Injection. The resultant solution will provide 20 mg/mL. AFTER RECONSTITUTION, FURTHER DILUTION IS REQUIRED."

Table 3. Identified Issues and Recommendations for Cidara Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
5.	As currently presented, there is no linear barcode included on your proposed container label.	The drug barcode is often used as an additional verification before drug preparation, administration, and/or dispensing in the hospital setting; therefore, it is an important safety feature that should be part of the label and is required per 21 CFR 201.25(c)(2).	Add the linear barcode to your proposed container label per 21 CFR 201.25(c)(2). Additionally, we recommend that the container label linear barcode be oriented in a vertical position, as a barcode placed in a horizontal position may be difficult to scan due to the curvature of the bottle. Furthermore, when determining placement of the linear barcode, consider that the barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode per 21 CFR 201.25(c)(i).
Carton Labeling			
1.	As currently presented, the intended location for the lot number and expiration date is not provided on the proposed carton labeling that was submitted.	The lot number statement is required on the carton labeling per 21 CFR 201.10(i)(1) and the product expiration date is also required on the carton labeling per 21 CFR 201.17. Additionally, clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the intended location of the lot number statement and expiration date on the carton labeling. When determining this placement, please ensure that there are no other numbers located in close proximity to the lot number or expiration date that can be mistaken as the lot number or expiration date. Additionally, to minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use for the expiration date. We recommend that the human-readable expiration date on the

Table 3. Identified Issues and Recommendations for Cidara Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash be used to separate the portions of the expiration date.
2.	As currently presented, the PDP does not include information regarding the need for reconstitution and further dilution of this product prior to administration.	We note that details regarding the need to reconstitute and further dilute this product currently appear on the side panel. However, we are concerned that this information could be missed by a healthcare provider preparing this product and could result in product preparation medication errors.	To increase the prominence and decrease the risk of overlooking this important information (i.e., the need to reconstitute and further dilute this product), we recommend that you include information regarding the need to reconstitute and further dilute this product prior to administration to the PDP. For example, "Must be reconstituted and further diluted."
3.	As currently presented, the human-readable and	The Drug Supply Chain Security Act (DSCSA)	We recommend that you review the guidance to

Table 3. Identified Issues and Recommendations for Cidara Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	machine-readable (2D data matrix barcode) product identifier is missing.	requires manufacturers and re-packagers, respectively, to affix or imprint a product identifier to the smallest saleable unit (usually the carton) of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format.	determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: *Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers* (July 2021).[c] Additionally, if the product identifier requirements apply to your product, we recommend you ensure there is sufficient white space between the linear barcode and 2-D matrix barcode to allow barcode scanners the ability to correctly read each barcode.
4.	As currently presented on the side panel, the terminology within the recommended dosage statement (i.e., (b) (4) is inconsistent with the terminology in the Prescribing Information."	The recommended dosage statement terminology should be consistent across the labeling to mitigate risk of confusion.	To ensure consistency with the Prescribing Information, we recommend revising the recommended dosage statement, (b) (4) See prescribing information" to "Recommended Dosage: See Prescribing Information."
5.	As currently presented, the side panel includes the recommended diluent (i.e., "sterile Water for Injection");	To minimize medication errors involving wrong dose, instructions for reconstituting the product and the resultant	To decrease the potential for wrong dose medication errors, revise the text on the carton labeling side panel to include volume of diluent (i.e., 9.5 mL)

[c] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act - Questions and Answers. 2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers.

Table 3. Identified Issues and Recommendations for Cidara Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	however, does not include the volume of diluent (i.e., 9.5 mL) for reconstituting the product or the resultant concentration (i.e., 20 mg/mL).	concentration (i.e., 20 mg/mL) should be included on the carton labeling. These instructions will inform persons responsible for preparing the product what type and volume of diluent should be used for reconstitution, and the amount of drug contained in each milliliter (mL) once reconstituted.	for reconstituting the product or the resultant concentration (i.e., 20 mg/mL). For example, "…reconstituted with 9.5 mL of Sterile Water for Injection. The resultant solution will provide 20 mg/mL. After reconstitution, further dilute with 0.9% Sodium Chloride Injection, USP (normal saline), 0.45% Sodium Chloride Injection, USP (half-normal saline), or 5% Dextrose Injection, USP as instructed in the prescribing information prior to intravenous infusion."

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Rezzayo that Cidara Therapeutics, Inc. submitted on July 22, 2022.

Table 4. Relevant Product Information for Rezzayo	
Initial Approval Date	N/A
Active Ingredient	rezafungin
Indication	For the treatment of candidemia and invasive candidiasis in adult patients.
Route of Administration	intravenous infusion
Dosage Form	for Injection
Strength	200 mg per vial
Dose and Frequency	Initial 400 mg loading dose, followed by a 200 mg dose once weekly thereafter.
How Supplied	Supplied as sterile white to pale yellow (b) (4) cake or powder in a single-dose 20 mL Type I glass vial with a stopper, an aluminum seal, and blue polypropylene flip-off cap. The vial stopper (b) (4) natural rubber latex. Packaging configuration: carton containing one 200 mg/vial.
Storage	Un-reconstituted vials should be stored at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature]. Excursions up to (b) (4)
Container Closure	Vial: (b) (4) 20 mm (b) (4) Type I glass vial Closure: 20 mm (b) (4) GRAY (b) (4) rubber stopper Seals: 20 mm aluminum seal with polypropylene flip off cap

APPENDIX F. LABELS AND LABELING

F.1 List of Label 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 Rezzayo labels and labeling submitted by Cidara Therapeutics, Inc..

- Container label received on July 22, 2022
- Carton labeling received on July 22, 2022
- Prescribing Information (PI) (Image not shown) received on July 22, 2022
    - Clean proposed (Draft) PI available from the following link: \\CDSESUB1\evsprod\nda217417\0001\m1\us\rezzayo-draft-label-text.docx.
    - Annotated PI available from the following link: \\CDSESUB1\evsprod\nda217417\0001\m1\us\rezzayo-uspi_annotated-word.docx.

F.2 Label and Labeling Images

Container label

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

Carton labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DEBORAH E MYERS
10/27/2022 09:08:43 AM

VALERIE S VAUGHAN
10/27/2022 09:52:23 AM