CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217417Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	217417
Applicant Name	Cidara Therapeutics, Inc.
Drug Product Name	REZZAYO® (rezafungin for injection)
Dosage Form.	Powder for reconstitution
Proposed Strength(s)	200 mg/vial
Route of Administration	Intravenous
Maximum Daily Dose	400 mg
Rx/OTC Dispensed	Rx
Proposed Indication	Treatment of candidemia and invasive candidiasis (IC)
Drug Product Description	Rezafungin was developed under a flexible development program due to the unmet needs for treatment of candidemia/IC, a serious infection that often impacts patients with multiple comorbidities and requires at least two weeks of systemic antifungal therapy. Rezafungin for injection is indicated for the treatment of candidemia and invasive candidiasis (IC) in patients 18 years of age or older who have limited or no alternative treatment options (a limited use indication). The drug product is a sterile (b) (4) powder for reconstitution and further dilution prior to intravenous infusion. Each single-dose vial of drug product contains rezafungin acetate equivalent to 200 mg rezafungin free base and inactive ingredients such as polysorbate 80, mannitol, histidine, (b) (4) hydrochloric acid and sodium hydroxide (b) (4) to adjust pH (b) (4)
Co-packaged product information	N/A
Device information:	N/A

Storage Temperature/ Conditions	20°C to 25°C (68°F to 77°F)		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Karina Zuck	Katherine Windsor
	Drug Product/ Labeling	Molly Lee	Dorota Matecka
	Manufacturing	Golam Kibria	James Norman/ Kshitij Patkar
	Biopharmaceutics	N/A	N/A
	Microbiology	Shannon Heine	Erika Pfeiler
	Other (specify):	N/A	N/A
	RBPM	Anh-Thy Ly	
	ATL	Dorota Matecka	
Consults	N/A		

2. Final Overall Recommendation - Approval with QPA(s)

3. Action Letter Information

a. Expiration Dating:

36 months at 20°C to 25°C (68°F to 77°F). Brief exposure to 15°C to 30°C (59°F to 86°F) permitted [see USP Controlled Room Temperature]

b. Additional Comments for Action

The proposed drug product, rezafungin for injection, is a sterile (b) (4) solid (cake or powder) supplied in a single-dose vial, which needs to be reconstituted and further diluted for intravenous infusion. As such, the drug product needs to

comply with applicable guidances and regulations to ensure that the excess solid in a vial is sufficient to allow for withdrawal and administration of the net container content of the drug product. Therefore, during the NDA review, the drug product specification was amended with two additional tests such as assay/gross content and assay of the drug product reconstituted solution (*for details, refer to the Drug Product Chapter, below*). It was agreed between the OPQ team and the Applicant that qualification and validation data for these additional tests would be provided via a postmarketing commitment (PMC). Therefore, the following CMC PMC should be included in the action letter:

PMC
Complete necessary qualification and validation studies of the current assay high-performance liquid chromatography (HPLC) analytical procedure to be used for the gross content and assay of reconstituted solution tests in the drug product specification. Update the relevant sections of Module 3 accordingly.

Final Report submission: 08/2023

The above change in the analytical procedures and validation of analytical data should be submitted as a CBE-0 supplement to your NDA.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug substance and the drug product (rezafungin for injection). The manufacturing and testing facilities have been found acceptable and an overall “Approve” recommendation was entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment (OPMA) on September 29, 2022. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate with QPAs**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**N/A**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): Yes

Comments:

Two comparability protocols (CPs) were submitted in the NDA:

(b) (4)

Both CPs were reviewed and found acceptable (b) (4)

Additional Lifecycle Comments: N/A

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VII: MICROBIOLOGY

IQA ANDA Assessment Guide Reference

Product Information	
NDA Number	217417
Assessment Cycle Number	1
Drug Product Name / Strength	Rezzayo rezafungin for injection, rezafungin acetate, 200 mg
Route of Administration	Intravenous infusion
Applicant Name	Cidara Therapeutics, Inc.
Therapeutic Classification/ OND Division	Type-1 New Molecular Entity / CDER/OND/OID/DAI
Manufacturing Site	Patheon, part of Thermo Fisher Scientific Viale G.B. Stucchi 110 20900 Monza (MB) Italy
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
Seq 0001 (1)	22 July 2022
Seq 0008 (8)	8 September 2022
Seq 0014 (14)	19 October 2022

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The subject drug product is a sterile (b) (4) powder for reconstitution and dilution prior to intravenous infusion. The 200 mg/vial product is supplied in a (b) (4) 20-mL Type I clear glass vial closed with a 20 mm (b) (4) rubber stopper and sealed with a 20 mm aluminum seal with a polypropylene flip-off cap. The application has been granted NME Original Priority, Fast Track, QIDP, and Orphan Designation.

Product quality microbiology deficiencies were conveyed to the applicant in a product quality microbiology Information Request, dated 3 October 2022.

The submission is recommended for approval from the standpoint of product quality microbiology.

Concise Description of Outstanding Issues: N/A

Supporting Documents:

- Microbiology Review of DMF (b) (4) ((b) (4) .*docx*), dated 27 June 2022 for (b) (4) information with regard to the (b) (4)
- Type V DMF (b) (4) for (b) (4)

Select Number of Approved Comparability Protocols: 0
Note: Two CP were included in the submission that pertain to (b) (4) These were not reviewed, as they are not relevant to product quality microbiology.

S DRUG SUBSTANCE

The drug substance is [redacted]

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product**
  (See Section 3.2.P.1, *Description and Composition of the Drug Product*)

  Rezafungin for injection is a sterile [redacted] powder for reconstitution and dilution prior to intravenous infusion.

- **Drug product composition**

Ingredient	Quantity per vial (mg)	Function
Rezafungin acetate	200	Active Ingredient
Polysorbate 80	450	[redacted]
Mannitol	500	
Histidine	47	
Hydrochloric acid	As needed	pH Adjuster
Sodium hydroxide	As needed	pH Adjuster
[redacted]		

- **Description of container closure system**
  (See Seq 0008 Section 3.2.P.7, pg. 2 of *Container Closure System*)

Component	Description	Manufacturer
Vial	[redacted] 20 mm [redacted] Type I glass vial	[redacted]
Closure	20 mm [redacted] GRAY [redacted] rubber stopper	
Seals	20 mm aluminum seal with polypropylene flip off cap	

Assessment: *Adequate*
The applicant provided an adequate description of the drug product composition and the container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

Container/Closure and Package Integrity

(See 3.2.P.5.3, *Validation of Analytical Procedures – Container Closure Integrity*)

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Recommendations were conveyed to the applicant.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	REZZAYO	Adequate
Established name(s)	(rezafungin for injection)	Adequate
Route(s) of administration	for intravenous use	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	For injection: 200 mg as a (b) (4) powder in a single-dose vial for reconstitution. (3)	Replace (b) (4) powder" with "solid" for consistency throughout the label
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Single-dose vial	Adequate

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	See below	Language was added, deleted or revised to increase readability and clarity. Language on visual inspection was revised to be consistent with the regulatory required verbatim statement for parenteral drug products. See 21 CFR 201.57 (c) (3). The terminology (b) (4) is recommended in place of "single-use". Refer to Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use, FDA Guidance for Industry for more information.

2.3 **Preparation for Administration**

(b) (4)

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1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	REZZAYO	Not adequate Revise to: For injection: 200 mg of rezafungin
Strength(s) in metric system	200 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance		Salt equivalent not listed as is consistent with salt policy
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	sterile white to pale yellow (b) (4) cake or powder	Remove (b) (4) and add solid (cake or powder) to simplify language and align with drug product specification
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Single-dose glass vial	Adequate

1.2.3 Section 11 (DESCRIPTION)

Reference ID: 5137232

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Established name is not present	"(rezafungin for injection)" should be added to section 11, as the established name should be present in Section 11.
Dosage form(s) and route(s) of administration	Not present	"(rezafungin for injection), for intravenous use" should be added to section 11, as the dosage form/route of administration should be present in Section 11.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	REZZAYO contains rezafungin acetate equivalent to 200 mg of rezafungin.	Section 11 should include a salt equivalency statement. Refer to Naming of Drug Products Containing Salt Drug Substances - Guidance for Industry. Revise to add amount of rezafungin acetate: REZZAYO contains 210 mg of rezafungin acetate equivalent to 200 mg of rezafungin
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	REZZAYO also contains 500 mg mannitol, 450 mg polysorbate 80, 47 mg histidine, and hydrochloric acid and/or sodium hydroxide for pH adjustment.	USP names are used. Per USP <1091>, the list of inactive ingredients should be revised to be in alphabetical order by name.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Name and quantities are listed. "for pH adjustment" is present.	Adequate

Reference ID: 5137232

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	REZZAYO is a sterile, (b) (4) product	
	(b) (4)	
Chemical name, structural formula, molecular weight	Rezafungin acetate is chemically designated as (b) (4)	Chemical name does not match the inverted USAN name in the USP dictionary.
	(b) (4)	
	The empirical formula of rezafungin acetate is $C_{63}H_{85}N_8O_{17} \cdot C_2H_3O_2$, and the formula weight is 1285.46 g/mol.	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	It is freely soluble in water, soluble in methanol, and sparingly soluble in ethanol.	Adequate

Reference ID: 5137232

For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., “synthesized and developed by Drug Company X,” “structurally unique molecular entity”	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	REZZAYO (rezafungin for injection)	Adequate
Strength(s) in metric system	**REZZAYO 200 mg**	Adequate
Available units (e.g., bottles of 100 tablets)	One 200-mg vial	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	as sterile white to pale yellow (b) (4) (b) (4) cake or powder	Revise for consistency with other sections of the label: Sterile white to pale yellow solid (cake or powder)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	**Single-Dose Vial of REZZAYO 200 mg**	Remove bolding and redundant language
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Brief storage statements for the reconstituted and diluted product with reference to Dosage and Administration section are included.	Adequate per the CDER labeling tool
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	

Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	REZZAYO (un-reconstituted) vials should be stored at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature]. (b) (4)	Revise to align with current labeling best practice: REZZAYO vials should be stored at 20°C to 25°C (68°F to 77°F). Brief exposure to 15°C to 30°C (59°F to 86°F) permitted (see USP Controlled Room Temperature).
Latex: (b) (4) "Not made with natural rubber latex. Avoid statements such as (b) (4)	The vial stopper (b) (4) natural rubber latex.	We recommend revisions to this statement based on best labeling practices. As shown, use the statement "Not made with natural rubber latex" (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) . See proposed edits.
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small

volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Yes	Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): N/A

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

3.2 Carton Labeling

Reference ID: 5137232

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Rezzayo (rezafungin for injection)	
Dosage strength	200 mg per vial	
Route of administration	For Intravenous Infusion Only	
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Vial contains rezafungin 200 mg (equivalent to 210 mg of rezafungin acetate)	
Injectable drug product: Inactive Ingredients stated	Inactive Ingredients: 500 mg mannitol, 450 mg polysorbate 80, (b) (4) mg histidine, and hydrochloric acid and/or sodium hydroxide for pH adjustment.	*Histidine amount should be listed as 47 mg according to 3.2.P.1 Description and Composition of the Drug Product
Net contents (e.g. tablet count)	Carton: 1 Sterile single-dose vial	
"Rx only" displayed on the principal display	Rx only is displayed once on container label and twice on carton ℞ only	
NDC number	Container and Carton: 82378-101-01	DMEPA comment: We recommend that you review the guidance to 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).[1] 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.

Lot number and expiration date	Not present on carton. Space indicated on container label, but format is not indicated.	DMEPA comments to address these issues
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 20°C to 25°C (68°F to 77°F) [redacted] (b) (4)	Store at 20°C to 25°C (68°F to 77°F). Brief exposure to 15°C to 30°C (59°F to 86°F) permitted (see USP Controlled Room Temperature).
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Carton: 1 Sterile Single-dose Vial Container: Not included	DMEPA comment to address missing package type from container label: 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." For example: "Single-Dose Vial – Discard Unused Portion"
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.		
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Not present on container label.	DMEPA comment to applicant: Add the linear barcode to your proposed container label per 21 CFR 201.25(c)(2).

[1] 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.

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Country of origin is UK **Manufactured by:** Patheon Italia S.p.A., a Thermo Fisher Scientific company Viale Gian Battista Stucchi 110 20900 Monza (MB) Italy **Distributed by:** Cidara Therapeutics, Inc. 6310 Nancy Ridge Drive, Suite 101 San Diego, CA 92121	Adequate
Medication Guide (if applicable)	N/A	
No text on Ferrule and Cap overseal	Yes	Adequate
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available		

Assessment of Carton and Container Labeling: OPQ Carton and Container Labeling recommendations were conveyed to the applicant with DMEPA comments in November 2022.

Overall Assessment and Recommendation:

OPQ Prescribing Information, Carton, and Container Labeling recommended revisions were conveyed to the applicant.

Primary Labeling Assessor Name and Date: Molly Lee, Ph.D., Branch 2, ONDP Division of New Drug Products I, 2/22/2023

Secondary Assessor Name and Date (and Secondary Summary, as needed): Dorota Matecka, Ph.D., ONDP Division of New Drug Products I, 2/22/2023

Molly Lee

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Dorota Matecka

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