CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206110Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)

NDA 206110 | Clinical Microbiology
Caspofungin Acetate for Injection | Kerian Grande Roche, PhD
Fresenius Kabi, USA, LLC

Date Company Submitted Document: 10-31-2016 | CDER Date Received: 10-31-2016
Received for Review: 10-31-2016 | Reviewer: Kerian Grande Roche
Date Assigned: 10-31-2016 | Date Complete: 12-15-2016

NAME AND ADDRESS OF SPONSOR

Fresenius Kabi USA, LLC
Three Corporate Drive
Lake Zurich, IL 60047

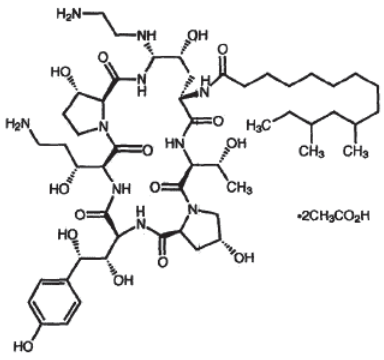
CONTACT PERSON

Jenna Holm
Regulatory Specialist
Fresenius Kabi USA, LLC
1-847-550-2647

DRUG PRODUCT NAME

Proprietary Name: None
Established Name/Code Name(s): Caspofungin Acetate for Injection
Chemical Name: 1-[(4 *R* ,5 *S*)-5-[(2-amino-ethyl)amino]- N^2 -(10, 12-dimethyl-1-oxotetradecyl)-4- hydroxy-Lornithine]-5-[(3 *R*)-3-hydroxy-L-ornithine] pneumocandin B_0 diacetate (salt).

Structural Formula:



Molecular weight:
1213.42

Empirical formula:
$C_{52}H_{88}N_{10}O15{\cdot}2C_2H_4O_2$

DRUG CATEGORY

Anti-fungal

NDA 206110 Clinical Microbiology
Caspofungin Acetate for Injection Kerian Grande Roche, PhD
Fresenius Kabi, USA, LLC

PROPOSED INDICATION(S)

Antifungal drug indicated in adults and pediatric patients (3 months and older) for:

- Empirical therapy for presumed fungal infections in febrile, neutropenic patients.
- Treatment of candidemia and the following *Candida* infections: intra-abdominal abscesses, peritonitis and pleural space infections.
- Treatment of esophageal candidiasis.
- Treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies (e.g., amphotericin B, lipid formulations of amphotericin B, itraconazole).

PROPOSED DOSAGE FORM, DOSAGE, ROUTE OF ADMINISTRATION, STRENGTH AND DURATION OF TREATMENT

Dosage Form: 50 or 70 mg lyophilized powder
Route of Administration: Intravenous administration
Dosage: 70 mg loading dose, 50 mg maintenance dose daily.
Strength: 50 mg/vial or 70 mg/vial
Duration of Treatment: at least (b) (4) days

DISPENSED

Rx

RELATED DOCUMENTS

NDA 21227

REMARKS

This 505(b)(2) NDA application is for caspofungin acetate for injection, 50 mg/vial and 70mg/vial. The reference listed drug is CANCIDAS® (caspofungin acetate), an echinocandin antifungal drug. Changes made to the proposed drug product from the reference listed drug are changes to inactive ingredients. This is a resubmission following pending litigation and tentative approval.

CONCLUSIONS AND RECOMMENDATIONS

From a clinical microbiology perspective, the recommendation is approval.

The Applicant submitted NDA 206110 on Dec. 27, 2013. No new clinical microbiology studies were submitted for review, however, labeling for the proposed drug product was submitted and reviewed. The clinical microbiology subsection (12.4) and references (15.0) of the Applicant's proposed labeling for caspofungin acetate for injection was in agreement with those sections in the labeling for the reference listed drug. Only minor formatting corrections were made and were reviewed on 12-27-13. The proposed labeling

is acceptable with no additional changes proposed at this time. A side-by side comparison of the proposed drug and the reference listed drugs is shown in the table below:

Table 1: Side-by-side comparison of the Reference Listed Drug and the proposed Drug

	Reference Listed Drug	Proposed Drug Product
Name	Cancidas®	Caspofungin Acetate for Injection
Conditions of Use (Indications)	Cancidas ® is indicated in adults and pediatric patients (3 months and older) for: Emperical therapy for presumed fungal infections in febrile, neutropenic patients; treatment of candidemia and the following Candida infections: intra-abdominal abscesses, peritonitis and pleural space infections; treatment of esophageal candidiasis; and treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies (e.g., amphotericin B, lipid formulations of amphotericin B, itraconazole).	Caspofungin Acetate for Injection is indicated in adults and pediatric patients (3 months and older) for: Emperical therapy for presumed fungal infections in febrile, neutropenic patients; treatment of candidemia and the following Candida infections: intra-abdominal abscesses, peritonitis and pleural space infections; treatment of esophageal candidiasis; and treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies (e.g., amphotericin B, lipid formulations of amphotericin B, itraconazole).
Dosage Form	Sterile, lyophilized product	Sterile, lyophilized product
Route of Administration	After reconstitution to either 5 mg/mL (for the 50 mg/vial presentation) or 7 mg/mL (for the 70 mg/vial presentation) as described in the package insert, administer by slow intravenous (IV) infusion over approximately 1 hour. Do not adminster by IV bolus administration. Do not mix or co-infuse with other intravenous substances, additives, or medications. Do not use diluents containing dextrose (α-D-Glucose).	After reconstitution to either 5 mg/mL (for the 50 mg/vial presentation) or 7 mg/mL (for the 70 mg/vial presentation) as described in the package insert, administer by slow intravenous (IV) infusion over approximately 1 hour. Do not adminster by IV bolus administration. Do not mix or co-infuse with other intravenous substances, additives, or medications. Do not use diluents containing dextrose (α-D-Glucose).
Active Ingredient (amount/vial, including overfill)	Caspofungin acetate: 54.6 mg/vial for the 50 mg/vial product code and 75.6 mg/vial for the 70 mg/vial product code	Caspofungin acetate: 54.6 mg/vial for the 50 mg/vial product code and 77.2 mg/vial for the 70 mg/vial product code
Strength	50 mg/vial and 70 mg/vial	50 mg/vial and 70 mg/vial

	Reference Listed Drug		Proposed Drug Product	
Excipients (amount/vial)	**50 mg/vial**	**70 mg/vial**	**50 mg/vial**	**70 mg/vial**
Arginine	N/A	N/A	100 mg/vial	140 mg/vial
Sucrose	39 mg/vial	54 mg/vial	N/A	N/A
Mannitol	26 mg/vial	36 mg/vial	N/A	N/A
				(b) (4)
Sodium Hydroxide, NF	(b) (4)		As required to adjust pH	
Bioequivalence	Refer to SECTION 1.12.15		Refer to SECTION 1.12.15	
Labeling	Refer to Section 1.14		Refer to Section 1.14	

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Source: This submission.

Kerian Grande Roche, Ph.D
Clinical Microbiology Reviewer

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/s/

KERIAN K GRANDE ROCHE
12/16/2016

TAMARA V FELDBLYUM
12/16/2016

NDA 206110 Clinical Microbiology Review #1
Caspofungin Acetate for Injection Kerian Grande Roche, PhD
Fresenius Kabi, USA, LLC

Date Company Submitted Document: 12-27-13 CDER Date Received: 12-27-13
Received for Review: 12-27-13 Reviewer: Kerian Grande Roche
Date Assigned: 12-27-13 Date Complete: 9-18-14

NAME AND ADDRESS OF SPONSOR
Fesenius Kabi USA, LLC
Three Corporate Drive
Lake Zurich, IL 60047

CONTACT PERSON
Jenna Holm
Regulatory Specialist
Fresenius Kabi USA, LLC
1-847-550-2647

DRUG PRODUCT NAME
Proprietary Name: None
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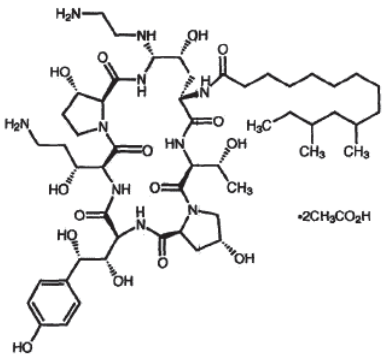

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Duration of Treatment: at least (b) (4) days

DISPENSED

Rx

RELATED DOCUMENTS

NDA 21227 (N-000, SE1-001, SE1-002, SE1-007, SE1-012)

REMARKS

This 505(b)(2) NDA application is for caspofungin acetate for injection, 50 mg/vial and 70mg/vial. The reference listed drug is CANCIDAS® (caspofungin acetate). Changes made to the proposed drug product from the reference listed drug are changes to inactive ingredients.

CONCLUSIONS AND RECOMMENDATIONS

No new clinical microbiology studies were submitted for review, however, labeling for the proposed drug product was submitted and reviewed. The clinical microbiology subsection (12.4) and references (15.0) of the Applicant's proposed labeling for caspofungin acetate for injection is in agreement with those sections in the labeling for the reference listed drug. Only minor formatting corrections have been made. Additionally, the proposed labeling is acceptable with no additional changes proposed at this time. A side-by side comparison of the proposed drug and the reference listed drugs is shown in the table below:

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Strength	50 mg/vial and 70 mg/vial	50 mg/vial and 70 mg/vial

	Reference Listed Drug		Proposed Drug Product	
Excipients (amount/vial)	**50 mg/vial**	**70 mg/vial**	**50 mg/vial**	**70 mg/vial**
Arginine	N/A	N/A	100 mg/vial	140 mg/vial
Sucrose	39 mg/vial	54 mg/vial	N/A	N/A
Mannitol	26 mg/vial	36 mg/vial	N/A	N/A
[redacted]				(b) (4)
Sodium Hydroxide, NF	(b) (4)		As required to adjust pH	
Bioequivalence	Refer to SECTION 1.12.15		Refer to SECTION 1.12.15	
Labeling	Refer to Section 1.14		Refer to Section 1.14	

Source: This submission.

Kerian Grande Roche, Ph.D
Clinical Microbiology Reviewer

Kerry Snow, MS
Clinical Microbiology Team Leader
18 September 2014

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/s/

KERIAN K GRANDE ROCHE
09/18/2014

KERRY SNOW
09/18/2014

Product Quality Microbiology Review

8/8/2014

NDA: 206110

Drug Product Name
Proprietary: N/A
Non-proprietary: Caspofungin Acetate Injection

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
12/27/2013	12/27/2013	1/02/2014	1/03/2014
3/4/2014	3/04/2014	N/A	N/A
6/24/2014	6/24/2014	N/A	N/A

Submission History (for 2nd Reviews or higher)
None

Applicant/Sponsor
Name: Fresenius Kabi, USA, LLC
Address: Three Corporate Dr. Lake Zurich, IL 60047
Representative: Jenna Holm
Telephone: 847-550-7120

Name of Reviewer: Steven P. Donald, M.S.

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original 505(b)(2) NDA

2. SUBMISSION PROVIDES FOR: Manufacture and marketing of a sterile drug product.

3. MANUFACTURING SITE: Fesenius Kabi USA, LLC, 3159 Staley Rd., NY 14072

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Dosage Form: Sterile, Lyophilized
- Route of Administration: Intravenous
- Strength/Potency: 50 mg/vial and 70 mg/vial
- Container: 10 ml/20 mm glass vial

5. METHOD(S) OF STERILIZATION: (b) (4) sterilization (b) (4)

6. PHARMACOLOGICAL CATEGORY: antifungal

B. SUPPORTING/RELATED DOCUMENTS: Type V DMF 011240 for manufacture of the drug product; DMF (b) (4). OGD Product Quality Microbiology DMF review (b) (4) mic11.doc, dated 8/07/2013. New Drugs Product Quality Microbiology DMF review D011240_2013Nov08_A1.doc, dated 4/16, 2014.

C. REMARKS:

A letter of Authorization is provided from Fresenius Kabi, dated 01 November, 2013 authorizing Fresenius Kabi USA, LLC to incorporate by reference information from DMF 011240 regarding to sterility assurance of the drug product manufactured at the FK, NY facility.

A letter of authorization is provided from (b) (4) dated 16 January, 2013, authorizing Fresenius Kabi, LLC, to incorporate by reference information from DMF (b) (4) The information is found in the last update to the DMF, dated 05. September, 2011: (b) (4) (b) (4)

This review was performed by Steven Donald with the exception of the 24 June 2014 amendment (reviewed by Bryan S. Riley).

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Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommended for Approval.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable -

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The bulk drug solution is

(b) (4)

B. Brief Description of Microbiology Deficiencies – N/A

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

D. Contains Potential Precedent Decision(s)- ☐ **Yes** ☒ **No**

III. Administrative

A. Reviewer's Signature _____

Bryan S. Riley, Ph.D.
Team Leader (acting)

B. Endorsement Block _____

Stephen Langille, Ph.D.
Senior Microbiology Reviewer

C. CC Block
N/A

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- Description of drug product –

White to off-white powder for reconstitution for IV infusion, available in 50 mg and 70 mg vials.

- Drug product composition –

Table 1. Drug product composition for 50 mg presentation

Drug Product Name	Content (per vial)	Function	Quality of Ingredient
Caspofungin Acetate	50 mg	Active Pharmaceutical Ingredient	Non-compendial
L-Arginine, USP	100 mg	(b) (4)	USP
(b) (4)			NF
			USP
Hydrochloric Acid, NF	As required	pH adjuster	NF
Sodium Hydroxide, NF	As required	pH adjuster	NF

(copied from description-and-composition.pdf, pg. 2)

The 70 mg strength contains Caspofungin70 mg, L-Arginine 140 mg, (b) (4) HCl (b) (4) ul; pH adjustment with HCl and NaOH.

Proposed maximum batch size:

- 50 mg/vial: (b) (4) L batch size
- 70 mg/vial: (b) (4) L batch size

- Description of container closure system –
  - Vial: 10 cc (b) (4) glass (b) (4) Type 1, 20 mm (b) (4), (b) (4).
  - Stopper: 20 mm (b) (4) rubber, (b) (4) (b) (4)

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- Container-Closure and Package integrity –

9 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT

Storage and Handling
The reconstituted product may be stored $\leq$ 25 ^{0}C for 1 hour, prior to the preparation of the infusion solution. The diluted product may be stored $\leq$ 25 ^{0}C for 24 hours; 2 – 8 ^{0}C for 48 hours.

Comment:
Reference is made to the Storage and Handling conditions identified in the product labeling. The following comment is provided in response to the applicant's plan to (b) (4) **between reconstitution of the final drug product and patient administration:**

Information Request of 3/11/2014:
Microbiological data should be provided in the NDA to demonstrate that the reconstituted product solution will not support microbial growth during the proposed storage period. Please provide a risk assessment summarizing studies that show adventitious microbial contamination does not grow under the storage conditions. Reference is made to Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products, Section 2.2.7.

Generally, "no growth" is interpreted as not more than a (b) (4) **increase from the initial count; however other evidence of growth may be significant. The test should be run at the label's recommended storage conditions, be conducted for 2 to 3-times the label's recommended storage period, and use the label-recommended fluids**

inoculated with low numbers ((b) (4) CFU/mL) of challenge microbes. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of these data, the product labeling should recommend that the post-constitution storage period is (b) (4) at room temperature or 24 hours under refrigerated conditions.

Response – 6/24/2014 amendment:
The amendment included Study Protocols PR-14-00073 and PR-14-00073A1 and the Final Report (attachment A). Hold time microbial studies for the drug product diluted in Lactated Ringers were performed up to (b) (4) hours at (b) (4) and (b) (4) hours (b) (4) (b) (4) The test organisms were from USP <51> (Antimicrobial Effectiveness Testing) and also *Arthrobacter psychrolactophilus* to represent a psychrophilic (cold loving) microbe. *Kocuria rhizophila* was added to the test organism panel for the (b) (4) incubation because of problems enumerating *Pseudomonas aeruginosa* (indeterminate results due to lack of discrete colonies on the surface of the solid medium). The results at each time point were acceptable (no increase over initial).

ADEQUATE

Comment – The hold time studies support the hold times for the diluted drug product as described in the product labeling.

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS: N/A

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/s/

BRYAN S RILEY
08/08/2014

STEPHEN E LANGILLE
08/08/2014

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 206110 **Applicant:** Fresenius Kabi USA, LLC **Letter Date:** 12/27/2013

Drug Name: Caspofungin Acetate for Injection **NDA Type:** 505(b)(2) **Stamp Date:** 12/27/2013

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	x		Section 3.2.P.2 contains (b) (4) validation and CCI testing results. 3.2.P.3.5 contains validation data.
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	x		Section 3.2.P.3.3
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	x		Section 3.2.P.3.5 DMF 011240 for the Grand Island, NY manufacturing facility
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		x	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?		x	The drug product is lyophilized and is not preserved.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	x		Section 3.2.P.5.1
7	Has the applicant submitted the results of analytical method verification studies?	x		Microbiological methods validation package is included.
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?			N/A
9	If sterile, are extended post-constitution and/or post-dilution hold times in the draft labeling supported by microbiological data?		x	Hold times for the reconstituted and diluted drug product may be excessive. Hold time issues will be addressed in the review of the

	Content Parameter	Yes	No	Comments
				NDA.
10	Is this NDA fileable? If not, then describe why.	x		

Additional Comments:

Steven Donald CDER/OPS/NDMS 1/9/2014

Reviewing Microbiologist Date

Stephen Langille CDER/OPS/NDMS 1/9/2014

Microbiology Secondary Reviewer/Team Leader Date

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/s/

STEVEN P DONALD
01/10/2014

STEPHEN E LANGILLE
01/10/2014