

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206110Orig1s000

OTHER REVIEW(S)

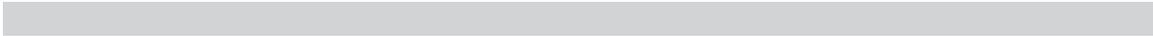
505(b)(2) ASSESSMENT

Application Information		
NDA # 206110	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Not submitted Established/Proper Name: Caspofungin Acetate for Injection Dosage Form: Sterile, lyophilized Strengths: 50 mg/vial, 70 mg/vial		
Applicant: Fresenius Kabi USA, LLC		
Date of Receipt: 12-27-2013		
PDUFA Goal Date: 10-27-2014		Action Goal Date (if different): 10-24-14
RPM: Alison Rodgers		
Proposed Indication(s): 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).		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
- YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
<i>Approved labeling for Cancidas, NDA 21227</i>	<i>Clinical pharmacology, safety and efficacy data</i>

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The sponsor’s request for a waiver for in-vivo bioavailability/bioequivalent studies has been granted.

The sponsor states that their product is identical to the reference listed drug except for the substitution of L-arginine in the sponsor’s product for sucrose and mannitol in Cancidas. The sponsor has provided analytical data comparing the proposed intravenous caspofungin product to the marketed Cancidas . Based on the analytical data, the sponsor expects the pharmacokinetics and pharmacodynamics profiles will not differ significantly from the marketed product. The sponsor’s product will be administered as IV solution using the same dosing regimen as Cancidas. The sponsor expects that the presence of L-arginine in its product will not significantly impact pharmacokinetics or pharmacodynamics.

The review is not yet complete, but based on discussion with the reviewer, it appears that the scientific bridge is adequate.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO
If “NO,” proceed to question #5.

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO”, proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES X NO

If “NO,” proceed to question #10.

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Cancidas	21227	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A X YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer “N/A”.

If “NO”, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES NO X

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES NO X

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES NO X

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES NO X

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a new formulation.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of

modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES X NO

If "NO" to (a) proceed to question #11.
If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES X NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A YES X NO

If this application relies only on non product-specific published literature, answer "N/A"

If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO X

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)? N/A YES NO

*If this application relies only on non product-specific published literature, answer "N/A"
If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 5514650, 5952300, 6136783

No patents listed *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES X NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

X 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s): 5378804, 5792746

- X 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): 5514650

Expiry date(s): 07/26/2015

- X 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

- 15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 5952300, 6136783

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES X NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES X NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): 06-30-14

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES X NO Patent owner(s) consent(s) to an immediate effective date of approval

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/s/

ALISON K RODGERS
12/30/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
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: December 27, 2016
Requesting Office or Division: Division of Anti- Infective Products (DAIP)
Application Type and Number: NDA 206110
Product Name and Strength: Caspofungin acetate for Injection,
50 mg per vial and 70 mg per vial
Submission Date: December 19 , 2016
Applicant/Sponsor Name: Fresenius Kabi USA, LLC (FK USA)
OSE RCM #: 2016-2752-1
DMEPA Primary Reviewer: Sevan Kolejian, PharmD
DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

The Division of Anti –Infective Products (DAIP) requested that we review the container labels and carton labeling for Caspofungin acetate for Injection, 50 mg per vial and 70 mg per vial (*See 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

The revised container labels and carton labeling for Caspofungin acetate for Injection, 50 mg per vial and 70 mg per vial, are acceptable from a medication error perspective.

We have no further recommendations at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

^a Kolejian, S. Label and Labeling Memorandum for Caspofungin (NDA 206110). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 DEC 13. OSE RCM No.: 2016-2752.

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/s/

SEVAN H KOLEJIAN
12/27/2016

BRENDA V BORDERS-HEMPHILL
12/27/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
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: December 13, 2016
Requesting Office or Division: Division of Anti- Infective Products (DAIP)
Application Type and Number: NDA 206110
Product Name and Strength: Caspofungin acetate for Injection,
50 mg per vial and 70 mg per vial
Submission Date: October 31, 2016
Applicant/Sponsor Name: Fresenius Kabi USA, LLC (FK USA)
OSE RCM #: 2016-2752
DMEPA Primary Reviewer: Sevan Kolejian, PharmD
DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

Labels and labeling submitted by Fresenius Kabi USA, LLC (FK USA) for Caspofungin acetate for Injection, 50 mg per vial and 70 mg per vial were previously reviewed and tentative approval for NDA 206110 was granted on November 20, 2015 due to pending litigation related to patent infringement. In this submission, the Applicant is seeking final approval of this NDA in anticipation of an outcome of the pending district court proceedings related to the expiry date of December 2016.

The Division of Anti –Infective Products (DAIP) requested that we review the container labels and tray/carton labeling for Caspofungin acetate for Injection, 50 mg per vial and 70 mg per vial (See Appendix A) to determine if they are acceptable from a medication error perspective.

2 CONCLUSION

DMEPA previously reviewed the container labels and tray labeling for Caspofungin acetate for Injection, 50 mg per vial and 70 mg per vial, NDA 206110, RCM No.: 2015-1560.^{a,b}

As part of the final approval, the Applicant resubmitted the container labels and tray/ carton labeling for Caspofungin acetate for Injection. However, since our last review, FK USA has updated container labels and tray labeling for Caspofungin acetate for Injection, 50 mg per vial and 70 mg per vial. FK USA states that the label and labeling have been updated per labeling revisions approved for reference listed drug (RLD), Cancidas, NDA 021227/S 034 & S 035. In addition to the RLD update, color layout and minor editorial revisions are also included (See *Appendix B*). We confirmed with Office of Product Quality (OPQ) reviewer that these editorial edits are acceptable from OPQ perspective. We determined that revisions to the NDC number is appropriate per CFR 21 207.35 (b)(3)(i). However, we determined that the proposed container labels and tray/carton labeling can be improved to increase clarity and prominence of important information to promote safe use of this product.

^a Kolejian, S. Review of Revised Label and Labeling Memorandum for Caspofungin (NDA 206110). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 Aug 18. OSE RCM No.: 2015-1560.

^b Kolejian, S. Review of Revised Label and Labeling Memorandum for Caspofungin (NDA 206110). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 SEP 11. OSE RCM No.: 2015-1560-1.

We recommend Fresenius Kabi implement these revisions below and include revised labels and labeling prior to approval of this NDA 206110.

3 RECOMMENDATIONS FOR FRESENIUS KABI USA, LLC

We recommend the following be implemented prior to approval of this NDA 206110:

A. Caspofungin acetate for Injection, 50 mg per vial

a) Container label:

1. Revise the statement on primary display panel (b) (4) to “For intravenous infusion after dilution”. We recommend this to minimize the risk of administering the drug as an intravenous bolus. You may accomplish this by relocating preservative free statement to the side panel.

b) Carton/tray labeling:

1. Remove (b) (4) quantity statement and revise the (b) (4) statement to read “10 single-dose vials” for clarity.

B. Caspofungin acetate for Injection, 70 mg per vial

a) Container label:

1. Revise the statement on primary display panel (b) (4) to “For intravenous infusion after dilution”. We recommend this to minimize the risk of administering the drug as an intravenous bolus. You may accomplish this by relocating preservative free statement to the side panel.

b) Carton/tray labeling:

2. Remove (b) (4) quantity statement and revise the (b) (4) statement to read “10 single-dose vials” for clarity.

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/s/

SEVAN H KOLEJIAN
12/13/2016

BRENDA V BORDERS-HEMPHILL
12/13/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
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: September 11, 2015

Requesting Office or Division: Division of Anti- Infective Products (DAIP)

Application Type and Number: NDA 206110; S- 017

Product Name and Strength: Caspofungin acetate for Injection,
50 mg per vial and 70 mg per vial

Product Type: Single ingredient

Rx or OTC: Rx

Applicant/Sponsor Name: Fresenius Kabi

Submission Date: September 3, 2015

OSE RCM #: 2015-1560-1

DMEPA Primary Reviewer: Sevan Kolejian, PharmD

DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

Fresenius Kabi submitted revised container labels in response to recommendations that we made during a previous label and labeling review.¹ The Sponsor inquired via an email communication dated August 26, 2015, whether the recommendation is warranted for the tray labeling. We clarified that since the statement “Single-Dose Vial – Discard Unused Portion” is more applicable for each vial, their approach to revise the statement only on the immediate container is reasonable. Furthermore, we clarified that when the Sponsor updates the container label and tray labeling with the company logo, we will need to review updated container label and tray labeling to ensure the added logo does not obstruct or distract from important information on the container label and tray labeling.

The Division of Anti –Infective Products (DAIP) requested that we review the revised container labels for Caspofungin acetate for Injection, 50 mg per vial and 70 mg per vial (Appendix A) to determine if they are acceptable from a medication error perspective. We reviewed the revised container labels and determined that the revisions are acceptable and the container label does not pose a safety risk from a medication error perspective.

2 CONCLUSIONS

The revised container labels are acceptable from a medication error perspective.

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APPENDIX A. LABEL AND LABELING SUBMITTED ON SEPTEMBER 3, 2015

¹ Kolejian, S. Review of Revised Label and Labeling Memorandum for Caspofungin (NDA 206110). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 Aug 18. OSE RCM No.: 2015-1560.

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/s/

SEVAN H KOLEJIAN
09/11/2015

BRENDA V BORDERS-HEMPHILL
09/14/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
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: August 18, 2015
Requesting Office or Division: Division of Anti- Infective Products (DAIP)
Application Type and Number: NDA 206110
Product Name and Strength: Caspofungin acetate for Injection,
50 mg per vial and 70 mg per vial
Product Type: Single ingredient
Rx or OTC: Rx
Applicant/Sponsor Name: Fresenius Kabi
Submission Date: July 24, 2015
OSE RCM #: 2015-1560
DMEPA Primary Reviewer: Sevan Kolejian, PharmD
DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

The Division of Anti –Infective Products (DAIP) requested that we review the container labels and tray labeling for Caspofungin acetate for Injection, 50 mg per vial and 70 mg per vial (Appendix A) to determine if they are acceptable from a medication error perspective.

2 CONCLUSIONS & RECOMMENDATIONS

DMEPA previously reviewed the container labels and tray labeling for Caspofungin acetate for Injection, 50 mg per vial and 70 mg per vial, NDA 206110, RCM No.: 2014-312 and recommended revisions.¹ The Applicant submitted revised labels and labeling, made the recommended revisions, and DMEPA determined that the Fresenius Kabi’s revisions were acceptable from a medication error perspective RCM No.: 2014-312.²

As part of class II resubmission, the Applicant resubmitted the container labels and tray labeling for Caspofungin acetate for Injection. We note that there are no changes to previously reviewed container labels and tray labeling. However, we determined that the proposed container labels and tray labeling can be improved to increase clarity and prominence of important information to promote safe use of this product.

We recommend Fresenius Kabi submit these revisions below and include labels and labeling prior to approval of this NDA 206110.

a) Container Label and Tray Labeling:

1. Revise the statement “Single Dose Vial” to read “Single-Dose Vial – Discard Unused Portion” to minimize risk of the entire contents of the vial being given as a single dose for pediatric patients.

If you have further questions or need clarifications, please contact Karen Townsend, OSE Project Manager, at 301-796-5413.

¹ Winiarski, A. Label and Labeling Review for Caspofungin (NDA 206110). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 July 11. 12 p. OSE RCM No.: 2014-312.

² Winiarski, A. Review of Revised Label and Labeling Memorandum for Caspofungin (NDA 206110). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 OCT 22. OSE RCM No.: 2014-312-1.

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/s/

SEVAN H KOLEJIAN
08/18/2015

BRENDA V BORDERS-HEMPHILL
08/19/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
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: October 22, 2014
Requesting Office or Division: Division of Anti-Infective Products (DAIP)
Application Type and Number: NDA 206110
Product Name and Strength: Caspofungin Acetate for Injection,
50 mg per vial and 70 mg per vial
Submission Date: September 2, 2014
Applicant/Sponsor Name: Fresenius Kabi
OSE RCM #: 2014-312-1
DMEPA Primary Reviewer: Aleksander Winiarski, PharmD
DMEPA Acting Team Leader: Tingting Gao, PharmD

1 PURPOSE OF MEMO

Division of Anti-Infective Products (DAIP) requested that we review the revised container labels and tray labeling (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSIONS

The revised container labels and tray labeling are acceptable from a medication error perspective.

¹ Winiarski A. Label and Labeling Review for Caspofungin (NDA 206110). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 July 11. 12 p. OSE RCM No.: 2014-312.

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ALEKSANDER P WINIARSKI
10/22/2014

TINGTING N GAO
10/22/2014

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

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

Memorandum

Date: September 11, 2014

To: Alison Rodgers, Regulatory Project Manager
Division of Anti-Infective Products

From: Christine Corser, Regulatory Review Officer
Office of Prescription Drug Promotion

Subject: **NDA #206110**
Caspofungin Acetate for Injection, for intravenous use

As requested in your consult dated March 26, 2014, OPDP has reviewed the proposed draft labeling for Caspofungin Acetate for Injection.

OPDP's comments on the PI are based on the substantially complete version of the labeling titled, "fk-draft-pi-word_052914.doc," which was received via email from DAIP on September 2, 2014.

OPDP's comments on the PI are provided in the attached, clean version of the labeling.

OPDP has also reviewed the proposed carton and container labels that were submitted to FDA on September 2, 2014 (50 mg Draft Vial and Tray Label & 70 mg Draft Vial and Tray Label). OPDP has no comments on the proposed carton and container labeling.

Thank you for the opportunity to review and provide comments on the proposed PI and carton/container labeling. If you have any questions about OPDP's comments, please contact Christine Corser at 6-2653 or Christine.corser@fda.hhs.gov.

43 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINE G CORSER
09/11/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 206110 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: Caspofungin Acetate for Injection Dosage Form: Sterile lyophilized Strengths: 50 mg/vial and 70 mg/vial		
Applicant: Fresenius Kabi USA, LLC Agent for Applicant (if applicable):		
Date of Application: 12-27-2013 Date of Receipt: 12-27-2013 Date clock started after UN: N/A		
PDUFA Goal Date: 10-27-2014		Action Goal Date (if different):
Filing Date: 2-25-2014		Date of Filing Meeting: 2-6-2014
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed indication(s)/Proposed change(s): Treatment of 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 <i>Candida</i> 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).		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): N/A				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p>X Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p>X Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<p><input type="checkbox"/></p>	<p>X</p>	<p><input type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>	<p><input type="checkbox"/></p>	<p>X</p>	<p><input type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>	<p><input type="checkbox"/></p>	<p>X</p>	<p><input type="checkbox"/></p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1623"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<p><input type="checkbox"/></p>	<p>X</p>	<p><input type="checkbox"/></p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>	<p><input type="checkbox"/></p>	<p>X</p>																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	X	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	X	<input type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	X	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	X	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	X	<input type="checkbox"/>		Pending submission of financial disclosure forms

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	X	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	X	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input type="checkbox"/>	X		No clinical studies conducted.
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	X	<input type="checkbox"/>		

Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>	X	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	X	Electronic submission
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	X	
Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<input type="checkbox"/>	X		

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input type="checkbox"/>	<input type="checkbox"/>	X	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	X	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	X	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input type="checkbox"/>	X	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RPM mailbox</i>	<input type="checkbox"/>	X	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X	<input type="checkbox"/>		
Is the PI submitted in PLR format? ⁴	X	<input type="checkbox"/>		

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 6, 2014

NDA #: 206110

PROPRIETARY NAME: NA

ESTABLISHED/PROPER NAME: Caspofungin Acetate for Injection

DOSAGE FORM/STRENGTH: Sterile lyophilized\ 50 mg/vial, 70 mg/vial

APPLICANT: Fresenius Kabi USA, LLC

PROPOSED INDICATION(S): Treatment of 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).

BACKGROUND: The sponsor submitted NDA 206110 on December 27, 2013 via the 505(b)(2) regulatory pathway. The reference listed drug (RLD) is Cancidas, NDA 21227, manufactured by Merck. The sponsor maintains that their product is identical to the RLD except for the substitution of L-arginine for sucrose and mannitol in Cancidas. The sponsor has requested a waiver from in vivo studies. No clinical studies were submitted. The sponsor is relying on the Agency's findings of safety and efficacy for the RLD to support the application.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Alison Rodgers	Y
	CPMS/TL:	Maureen Dillon-Parker	Y
Cross-Discipline Team Leader (CDTL)	Thomas Smith		Y
Clinical	Reviewer:	Hala Shamsuddin	Y
	TL:	Thomas Smith	Y

Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	Kerian Grande	Y
	TL:	Kerry Snow	N
Clinical Pharmacology	Reviewer:	Dakshina Chilukuri	Y
	TL:	Philip Colangelo	Y
Biostatistics	Reviewer:	Cheryl Dixon	Y
	TL:	Karen Higgins	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Owen McMaster	Y
	TL:	Wendy Schmidt	Y
Product Quality (CMC)	Reviewer:	Lin Qi	Y
	TL:	Dorota Matecka	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Steven Donald	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Aleksander Winiarski	Y
	TL:		
Other reviewers	Houda Mahayni (ONDQA Biopharmaceutics)		Y
Other attendees	Joseph Toerner, Sumathi Nambiar, Katherine Laessig		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues: 	<input type="checkbox"/> Not Applicable
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<ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO The sponsor has requested a waiver for in-vivo bioavailability/ bioequivalence studies. Analytical and literature based data has been provided. The sponsor states that their product is identical to the reference listed drug except for the substitution of L-arginine for sucrose and mannitol in Cancidas. The sponsor has provided analytical data comparing the proposed intravenous caspofungin product to the marketed Cancidas. Based on the analytical data, the sponsor expects the pharmacokinetics and pharmacodynamics profiles will not differ significantly from the marketed product. The sponsor’s product will be administered as IV solution using the same dosing regimen as Cancidas. The sponsor expects that the presence of L-arginine in its product will not significantly impact pharmacokinetics or pharmacodynamics.
<ul style="list-style-type: none"> ● Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> ● Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> ● Clinical study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p>If no, explain: No clinical studies conducted.</p>	
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments: Nothing new to review.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments: No new information added to label.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments: No clinical studies; nothing to review.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments: Nothing new to review.</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments: Will have comments for 74-day letter regarding storage and handling.</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments: The drug product manufacturer has significant GMP issues; Office of Compliance has been consulted.</p>	<p><input type="checkbox"/> Not Applicable</p> <p>X YES <input type="checkbox"/> NO</p> <p>X YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p>X Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<p>X N/A</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	

<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Sumathi Nambiar, MD, MPH</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 5/22/14</p> <p>21st Century Review Milestones () (listing review milestones in this document is optional): Mid-Cycle: 5/22/14, Wrap-Up: 9/18/14</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. X Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> X Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
X	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).

<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
X	Send review issues/no review issues by day 74
X	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALISON K RODGERS
08/13/2014

MAUREEN P DILLON PARKER
08/26/2014

**REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 206110

Application Type: New NDA

Name of Drug/Dosage Form: Caspofungin Acetate for Injection

Applicant: Fresenius Kabi USA, LLC

Receipt Date: 12-27-13

Goal Date: 10-27-14

1. Regulatory History and Applicant's Main Proposals

The sponsor submitted NDA 206110 as a 505(b)(2) application. The reference listed drug is Cancidas, NDA 21227.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by April 1, 2014. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between

Selected Requirements of Prescribing Information

the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- NO** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment: *The Highlights Limitation Statement is not bolded. The drug product name is not in upper case letters.*

Product Title in Highlights

- NO** 10. Product title must be **bolded**.

Selected Requirements of Prescribing Information

Comment: *Product title is not bolded.*

Initial U.S. Approval in Highlights

- NO** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment: *The Initial U.S. Approval in HL is not bolded.*

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- YES** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- YES** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- YES** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES

Selected Requirements of Prescribing Information

19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *Revision date should be bolded and the date listed in mo/year format.*

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

Selected Requirements of Prescribing Information

- NO** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.
- Comment:** The corresponding new or modified text in the FPI subsection is not marked with a vertical line on the left edge.*

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- YES** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

N/A

Selected Requirements of Prescribing Information

41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- N/A**
42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

ALISON K RODGERS

08/12/2014

MAUREEN P DILLON PARKER

08/26/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
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: July 11, 2014
Requesting Office or Division: Division of Anti-Infective Products (DAIP)
Application Type and Number: NDA 206110
Product Name and Strength: Caspofungin Acetate for Injection,
50 mg per vial and 70 mg per vial
Product Type: Single Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Fresenius Kabi
Submission Date: December 27, 2013
OSE RCM #: 2014-312
DMEPA Primary Reviewer: Aleksander Winiarski, PharmD
DMEPA Acting Team Leader: Tingting Gao, PharmD

1 REASON FOR REVIEW

Fresenius Kabi developed a new formulation of Caspofungin Acetate for Injection, 50 mg per vial and 70 mg per vial under NDA 206110. This is a 505(b)(2) application and Fresenius Kabi referred the listed drug, Cancidas (Caspofungin Acetate) for Injection, 50 mg per vial and 70 mg per vial, NDA 021227.

The Division of Anti-Infective Products (DAIP) requested that we review the submitted Caspofungin Acetate labels and labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	D - N/A
ISMP Newsletters	E
Other	F - N/A
Proposed Labels and Labeling	G

N/A = Not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We identified 7 medication error cases in the FAERS database that may be relevant to the submitted labels or labeling (See Appendix B2). Of the identified 7 medication error cases, 2 were wrong dose (foreign cases), 1 was wrong administration technique involving a faster infusion than recommended (US case), and 4 were wrong technique in product preparation (3 foreign cases – wrong dilution solution used and 1 US case – incorrect reconstitution volume used).

We evaluated the submitted Caspofungin Acetate prescribing information (PI) labeling and identified that the PI labeling clearly states the correct dosing and clearly describe the administration technique and product preparation. Additionally, we note that 5 of the 7 medication error cases were foreign and it is unclear how prominent this information is listed in foreign PI labeling. Therefore, we conclude that the submitted PI labeling is adequate to minimize the risk for these errors. Also, in our review we identified the use of symbols such as ‘≤’, ‘>’, ‘≥’, and ‘IV’¹, in the Dosage and Administrations sections and How Supplied section of the PI labeling, which should be replaced with the corresponding words.

The container labels and carton labeling contain the following statement (b) (4), which could be misinterpreted as for intravenous injection. The correct administration technique for this product is via intravenous infusion. Therefore, to reflect the correct usage and for consistency with the Dosage and Administration sections of the PI labeling, we recommend that the use statement (b) (4) be revised to “For Intravenous Infusion Only”.

Additionally, in our review of the submitted labels and labeling, we identified some potential readability issues. We provide specific recommendations in sections 4.1 and 4.2 below.

4 CONCLUSION & RECOMMENDATIONS

The submitted labels and labeling for Caspofungin Acetate may be improved to communicate important use information and to improve prominence of product information. We recommend the following revisions be implemented prior to approval of the NDA.

4.1 RECOMMENDATIONS FOR THE DIVISION

DMEPA provides the following comments for the Division’s consideration

A. Dosage and Administration Sections and How Supplied Section, Highlights of Prescribing Information and Full Prescribing Information

1. We note the use of symbols, such as: ‘≤’, ‘>’, ‘≥’, and ‘IV’¹, in the Dosage and Administrations sections of the PI labeling. Consider replacing the symbols with the corresponding words, such as ‘≤’ with “less than or equal to”, ‘>’ with “greater than”, ‘≥’ with “greater than or equal to”, and ‘IV’ with “intravenous”, for clarity.

¹ FDA Guidance for Industry: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*.

2. To improve readability, consider listing the diluents in Section 2.6 in bullet point.
For example:

Aseptically add 10.8 mL of one of the following diluents to the vial:

- 0.9% Sodium Chloride Injection, or
- Sterile Water for Injection, or
- Bacteriostatic Water for Injection with methylparaben and propylparaben, or
- Bacteriostatic Water for Injection with 0.9% benzyl alcohol

4.2 RECOMMENDATIONS FOR FRESENIUS KABI

DMEPA recommends the following revisions prior to approval of the NDA:

A. All Container Labels and Carton (Tray) Labeling

1. The correct administration technique for the product is via intravenous infusion; therefore, revise the statement [REDACTED] ^{(b) (4)} to “For Intravenous Infusion Only” This revision will also be consistent with the information provided in the Dosage and Administration sections of the Prescribing Information (PI) labeling.
2. To improve readability, revise the letter case of the established name “CASPOFUNGIN ACETATE” from all capitals to title case, “Caspofungin Acetate”.
3. The container label of one unit and the carton labeling of 10 units should have different NDC numbers. Consider revising the NDC numbers so that the carton labeling and vial label NDC numbers are different for these two package configurations.
4. To improve readability and if space permits, consider adding white space between the statement “Each vial contain xx mg of Casopfungin...” and “Reconstitute with 10.8 mL for diluent”
5. The significance of the following numbers is unclear: [REDACTED] ^{(b) (4)}
[REDACTED]
[REDACTED]

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Caspofungin Acetate from the submitted insert labeling on April 1, 2014.

Table 2. Relevant Product Information for Caspofungin Acetate	
Active Ingredient	Caspofungin Acetate
Indication	<p>Caspofungin acetate for injection is indicated in adults and pediatric patients (3 months and older)</p> <ul style="list-style-type: none"> • Empirical therapy for presumed fungal infections in febrile, neutropenic patients • Treatment of candidemia and the following <i>Candida</i> infections: intra-abdominal abscesses, peritonitis and pleural space infections. Caspofungin acetate for injection has not been studied in endocarditis, osteomyelitis, and meningitis due to <i>Candida</i>. • 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). Caspofungin acetate for injection has not been studied as initial therapy for invasive aspergillosis.
Route of Administration	Intravenous Infusion
Dosage Form	Injection, powder for solution
Strengths	50 mg per vial and 70 mg per vial
Dose and Frequency	<p>Adults: usual dose 70 mg loading, 50 mg daily maintenance</p> <p>Children: Loading dose 70 mg/m², maintenance 50 mg/m² daily, if it is well tolerated but does not provide an adequate clinical response, the daily dose can be increased to 70 mg/m² daily (not to exceed 70 mg).</p>
How Supplied	Caspofungin Acetate for Injection is supplied in single-use vials, packaged in trays of 10.
Storage	Room temperature
Container Closure	Glass vial

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on June 30, 2014 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.²

Date Range	April 21, 2008* to June 30, 2014 *Date of last FAERS search in previous relevant OSE review # 2008-570
Product	Caspofungin, Caspofungin Acetate [product active ingredient] Candidas [product name]
Event (MedDRA Terms)	Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Quality Issues (NEC)[HLT]

B.2 Results

Our search identified 28 cases, of which 7 described errors relevant for this review.

Of the identified 7 medication error cases, 2 were wrong dose, 1 was wrong administration technique, and 4 were wrong technique in product preparation.

Wrong dose (n=2)

We identified 2 wrong dose cases. Both of the cases were foreign, therefore it is unclear how relevant these cases are to the US prescribing information (PI) labeling.

The first case described a 16 year old patient who was dosed based on Body Surface Area (BSA), which is consistent with US PI labeling. Based on the calculation the patient received 110 mg as a loading dose, then 80 mg for the maintenance dose, which was reported as an overdose. The case stated that the “maximum dosage was overlooked”, indicating similar maximum doses to the US PI for pediatric patients. The patient experienced hypotensive shock and was recovering at the time of the report. The US PI labeling clearly states that the maximum dose in pediatric

² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

patient is 70 mg, regardless of BSA calculation, and it's unclear how prominent the maximum pediatric dose is presented in the foreign PI. No further details relevant to the root cause of the error were provided.

The second case described a 65 year old patient who was receiving concomitant anti-tuberculosis multi-drug therapy, which included Rifampin. The patient was septic, caused by multiple infectious organisms. Caspofungin was selected for the fungal infection at a standard loading dose of 70 mg and then 50 mg as a maintenance dose. However, because of the concomitant therapy with Rifampin, according to the US PI and submitted Caspofungin PI, the correct maintenance dose should have been 70 mg daily. The case reported that the 50 mg dose was an under dose, which lead to therapeutic failure. The patient died due to multi-organism sepsis, multi-organ failure and shock. The US PI labeling clearly states that the correct maintenance dose is 70 mg for patients who are on concomitant Rifampin therapy and it's unclear how prominent this information is presented in the foreign PI. No further details relevant to the root cause of the error were provided.

Wrong Administration Technique (n=1)

One US case described wrong administration technique. According to the patient's family member, a single infusion of the Caspofungin was administered over approximately 35 minutes instead of 1 hour that is specified in the PI labeling. Therapy with Caspofungin was discontinued, however the patient continued to suffer from "swelling on the brain" from which she had not recovered. No relevant information to the root cause of the error was provided. The Candida US PI and Caspofungin submitted PI clearly state that Caspofungin is to be administered via slow intravenous infusion over approximately 1 hour.

Wrong technique in product preparation (n=4)

We identified 4 cases that describe wrong technique in product preparation. Three of the cases were foreign and describe mixing Caspofungin in a wrong solution (dextrose/glucose and one only described as potentially wrong). Errors resulted in: no outcome, patient being observed, and one prolonged hospitalization. No relevant information to the root cause of the error was provided. The Candida US PI, the submitted PI labeling and submitted carton clearly state that Caspofungin is not to be mixed with dextrose solutions and the PI provides information for compatible solutions. It's unclear how prominent this information is presented in the foreign labeling; therefore it is unclear how relevant these cases are to the US prescribing information (PI) labeling.

The final wrong technique case is domestic and describes an incorrect volume used to reconstitute the 50 mg vial (10.5 mL vs. 10.8 mL specified in the PI labeling). The case did not specify any relevant information to the root cause of the error and no patient outcomes were reported. Table 1 in the Dosage and Administration sections of the Candida and submitted

Caspofungin PI labeling clearly state that 10.8 mL is the correct volume to reconstitute each vial. It's unclear if this is a true medication error (b) (4) and it is unknown which product was used.

We excluded 21 cases because they were either not relevant to the submitted NDA for Caspofungin Acetate Injection or because they did not provide evaluable information or because they did not describe a medication error related to US labels or labeling. The excluded cases describe:

- Accidental exposure (n=1)
- Duplicate case (n=2)
- Error related to another suspect drug (n=9)
- No medication errors occurred
 - Use of existing central line to administer the drug (n=1)
 - Foreign case suggesting that obese patient should receive a higher dose (n=1)
- Off label use (foreign cases) - Various non-US approved dosing regimens and doses (n=7)

B.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

Case #	Vrsn	ME category	Country	MFR Ctrl #	Case Type
7016289	1	wrong administration technique – infused too quickly	USA	US-MERCK-0906USA00860	Expedited (15-Day)
7038897	2	wrong technique in product preparation - foreign	NZL	NZ-MERCK-0905NZL00008	Expedited (15-Day)
7895569	2	wrong dose selection based on pediatric BSA dosing	CAN	CA-MERCK-1104USA01011	Expedited (15-Day)
8025702	4	wrong dose based on known drug interaction	ESP	ES-MERCK-1107ESP00003	Expedited (15-Day)

9289845	1	wrong technique in product preparation - foreign	GBR	GB-MERCK-1305GBR006635	Expedited (15-Day)
9643826	1	wrong technique in product preparation - foreign	DEU	DE-009507513-1310DEU007802	Expedited (15-Day)
9669528	1	wrong technique in product preparation - no outcomes or root cause	USA	US-009507513-1310USA014618	Non-Expedited

B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:drive on June 30, 2014 using the terms Caspofungin Acetate or Cancidas to identify reviews previously performed by DMEPA.

C.2 Results

Our search identified one previous review², and we confirmed that our previous recommendations were implemented or considered.

The review identified similar medication errors to the errors identified in this review. We note that we did not identify any new US cases of wrong technique in product preparation involving

² Crandall A. Medication Error Review for Cancidas (Caspofungin Acetate) injection (NDA 021227). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); July 9, 2008. OSE RCM No.: 2008-570.

wrong dilution solutions (3 foreign cases were identified) for Cancidas. [REDACTED]

(b) (4)

[REDACTED] and that both the current Cancidas carton and the submitted carton for Caspofungin Acetate contain the boxed warning statement “Do Not Use Diluents Containing Dextrose”.

APPENDIX E. ISMP NEWSLETTERS

E.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on June 30, 2014 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community/Ambulatory Care
Search Strategy and Terms	Match Any of the words: Caspofungin, Cancidas

E.2 Results

Our search did not identify any ISMP Medication Safety Alerts.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,³ along with postmarket medication error data, we reviewed the following Caspofungin Acetate labels and labeling submitted by Fresenius Kabi December 27, 2013.

G.2 Label and Labeling Images

³ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALEKSANDER P WINIARSKI
07/11/2014

TINGTING N GAO
07/14/2014