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RESEARCH**

APPLICATION NUMBER:

206110Orig1s000

SUMMARY REVIEW

Division Director Summary Review

Date	(electronic stamp)
From	Sumathi Nambiar MD MPH
Subject	Division Director Review
NDA #	206110
Applicant	Fresenius Kabi USA, LLC
Date of Re-submission (Class I)	October 31, 2016
PDUFA Goal Date	December 31, 2016
Established (USAN) names	Caspofungin acetate for injection* (caspofungin acetate)
Dosage forms/Strength	Powder for injection, 50 mg/vial and 70 mg/vial
Proposed Indication(s)	<ol style="list-style-type: none"> 1. Empirical therapy for presumed fungal infections in febrile, neutropenic patients 2. Treatment of candidemia and the following <i>Candida</i> infections: intra-abdominal abscesses, peritonitis, and pleural space infections 3. Treatment of esophageal candidiasis 4. Treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies
Action	Approval

** No proprietary/trade name was proposed for the drug product*

This 505(b)(2) NDA submitted by Fresenius Kabi USA, LLC provides for a new injectable formulation of caspofungin acetate. The listed drug is Cancidas (caspofungin acetate) for Injection, 50 mg/vial and 70 mg/vial (NDA 21227). The excipients in the proposed drug product include arginine and sodium hydroxide/hydrochloric acid whereas the listed drug includes sucrose, mannitol and glacial acetic acid.

The NDA was originally submitted on December 27, 2013. On October 21, 2014, a complete response action was taken due to several product quality deficiencies. These deficiencies were adequately addressed in the first resubmission dated May 27, 2015. Due to pending patent issues, the NDA was tentatively approved on November 20, 2015. The current resubmission contains minor updates to labeling to be consistent with the revisions made to the listed drug.

For a detailed review of this NDA, please refer to previous reviews from the review team and the cross-discipline team leader (CDTL). This memo will only address issues pertinent to this resubmission. All reviewers and the CDTL recommend approval of this NDA.

The manufacturing facilities have been found to be in current Good Manufacturing Practice (cGMP) compliance by the Office of Process and Facilities (review dated November 18, 2016).

The following patents are currently listed in the Orange Book for the listed drug Cancidas¹:

- US Patent No. 5,514,650*PED - Expiry Date: July 26, 2015
- US Patent No. 5,952,300 - Expiry Date: March 28, 2017
- US Patent No. 5,952,300*PED - Expiry Date: September 28, 2017
- US Patent No. 6,136,783 - Expiry Date: March 28, 2017
- US Patent No. 6,136,783*PED - Expiry Date: September 28, 2017

Fresenius Kabi USA, LLC has submitted a Paragraph IV certification for the above patents in the NDA and also certified that the Paragraph IV certification notices had been delivered to the listed drug patent and NDA holders (Merck & Co., Inc. and Merck Sharp & Dohme Corp.). On August 14, 2014, the Applicant notified the Agency that Merck & Co. Inc. and Merck Sharp and Dohme Corp. had filed suit against Fresenius Kabi USA, LLC for patent infringement for patents 5,514,650 and 5,952,300. On November 13, 2014, the Applicant submitted an amendment to convert the Paragraph IV certification for Patent No. 5,514,650 to a Paragraph III certification.

The expiration date of the 30-month stay is December 30, 2016, and, therefore, the Applicant is seeking approval of the NDA pending district court proceedings by expiry of the 30-month stay date on December 30, 2016.

The labeling recommendations from the review team have been incorporated in the proposed package insert and container labels.

I concur with the assessments made by the review team and the CDTL that this NDA be approved.

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http://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=021227&Appl_type=N; accessed December 29, 2016

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/s/

SUMATHI NAMBIAR
12/30/2016

Division Director Decisional Memo

Date	(electronic stamp)
From	Sumathi Nambiar MD MPH
Subject	Division Director Decisional Memo
NDA #	206110
Applicant Name	Fresenius Kabi USA, LLC
Date of Submission	May 27, 2015
PDUFA Goal Date	November 27, 2015
Established (USAN) Name	Caspofungin Acetate for Injection
Dosage Forms / Strength	Powder for injection, 50 mg/vial and 70 mg/vial
Proposed Indications	<ol style="list-style-type: none"> 1. Empirical therapy for presumed fungal infections in febrile, neutropenic patients 2. Treatment of candidemia and the following <i>Candida</i> infections: intra-abdominal abscesses, peritonitis, and pleural space infections 3. Treatment of esophageal candidiasis 4. Treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies
Recommended Action:	Tentative Approval

1.0 Introduction

NDA 206110, Caspofungin Acetate for Injection, 50 mg/vial and 70 mg/vial submitted by Fresenius Kabi USA, LLC, provides for a new formulation of injectable caspofungin to be used for the treatment of the same indications as listed in the labeling for Cancidas® (caspofungin). This NDA was submitted as a 505(b)(2) application and the listed drug is Cancidas® (caspofungin) Injection, 50 mg/vial and 70 mg/vial, held by Merck (NDA 21227). Cancidas is approved for the treatment of adults and pediatric patients (3 months and older) for the following indications:

1. Empirical therapy for presumed fungal infections in febrile, neutropenic patients
2. Treatment of candidemia and the following *Candida* infections: intra-abdominal abscesses, peritonitis, and pleural space infections
3. Treatment of esophageal candidiasis
4. 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).

2.0 Background

The proposed drug product, Caspofungin Acetate for Injection, 50 mg/vial and 70 mg/vial is a new formulation of caspofungin for injection. The drug product differs from the listed drug in that it contains arginine and sodium hydroxide/hydrochloric acid whereas the listed drug formulation includes sucrose, mannitol and glacial acetic acid. A Complete Response (CR) letter was issued on October 14, 2014, due to Product Quality deficiencies and an overall withhold recommendation for facilities. In the current submission, the Applicant has responded to the deficiencies noted in the CR letter.

For a detailed discussion of NDA 206110, please refer to discipline specific reviews in the previous review cycle, the Product Quality review of the resubmission and the Cross-Discipline Team Leader Review. This review will focus only the issues addressed in the resubmission.

3.0 Product Quality

The Product Quality reviewer for the resubmission is Dorota Matecka, PhD. Dr. Matecka notes that the deficiencies listed in the CR letter have been addressed satisfactorily. DMF (b) (4) referenced for the caspofungin drug substance was found to be adequate to support this NDA. The resubmission includes 24-month room temperature stability data for the three registration batches of the drug product (both strengths). The proposed expiration dating of 24 months and the room temperature storage conditions have been found acceptable for the proposed drug product. In addition, all manufacturing facilities for the drug substance and the drug product have been found acceptable by the Office of Process and Facilities.

Dr. Matecka recommends approval of the NDA and I agree with her assessment.

4.0 Clinical Efficacy/Safety

Hala Shamsuddin, MD, is the clinical reviewer for this application. No new clinical studies were submitted in this NDA. No new safety issues were identified in the literature. Dr. Shamsuddin recommends approval of the NDA with the labeling revisions relevant to this drug product.

5.0 Labeling

Sevan Kolejian, PharmD, from the Division of Medication Error Prevention and Analysis performed a review of the container labels and found them acceptable. Dr. Kolejian's recommendations for labeling revisions have been incorporated. Christine Corser, Pharm D, from the Office of Prescription Drug Promotion provided labeling revisions that have been incorporated in labeling. Revisions have been made to the Dosage and Administration, Description, and How Supplied Sections of the package insert to reflect the differences between this product and the listed drug.

6.0 Pediatrics

Under the Pediatric Research and Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless the requirement is waived, deferred or inapplicable. As none of these criteria are applicable, this NDA is exempt from PREA requirements.

7.0 Other Regulatory Issues

The reference listed application, NDA 21227, Cancidas® (caspofungin) Injection, has the following unexpired patents listed in the Orange Book:

- US Patent No. 5,952,300 - Expiry Date: March 28, 2017
- US Patent No. 5,952,300*PED - Expiry Date: September 28, 2017
- US Patent No. 6,136,783 - Expiry Date: March 28, 2017
- US Patent No. 6,136,783*PED - Expiry Date: September 28, 2017

Fresenius Kabi USA, LLC has submitted Paragraph IV certification for the above patents. On July 9, 2014, the Applicant notified the Agency that on June 30, 2014, the Paragraph IV certification notices were delivered to the listed drug patent and NDA holders. On August 14, 2014, the Applicant notified the Agency that Merck & Co. Inc. and Merck Sharp and Dohme Corp. have filed suit against Fresenius Kabi USA, LLC for patent infringement for patents 5,514,650 and 5,952,300.

On November 13, 2014, the Applicant submitted an amendment to convert the paragraph IV certification for Patent No. 5,514,650 to a Paragraph III certification. Per the Orange Book, this patent inclusive of the six month pediatric exclusivity expired on July 26, 2015.

8.0 Recommended Regulatory Action

I agree with the recommendations made by the review team and the CDTL that the NDA be approved. Due to outstanding issues regarding patents, the application will receive a tentative approval at this time.

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/s/

SUMATHI NAMBIAR
11/20/2015

Division Director Decisional Memo

Date	(electronic stamp)
From	Sumathi Nambiar MD MPH
Subject	Division Director Decisional Memo
NDA #	206110
Applicant Name	Fresenius Kabi USA, LLC
Date of Submission	December 27, 2013
PDUFA Goal Date	October 27, 2014
Established (USAN) Name	Caspofungin Acetate for Injection
Dosage Forms / Strength	Powder for injection, 50 mg/vial and 70 mg/vial
Proposed Indications	<ol style="list-style-type: none"> 1. Empirical therapy for presumed fungal infections in febrile, neutropenic patients 2. Treatment of candidemia and the following <i>Candida</i> infections: intra-abdominal abscesses, peritonitis, and pleural space infections 3. Treatment of esophageal candidiasis 4. Treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies
Recommended Action:	Complete Response

Material Reviewed/Consulted	Names of Discipline Reviewers
Action Package including:	
Pharmacology Toxicology Review	Owen McMaster PhD
Chemistry Manufacturing and Controls Review	Lin Qi PhD
Quality Biopharmaceutics Review	Houda Mahayni PhD
Cross-Discipline Team Leader Review	Dorota Matecka PhD
Medical Officer Review	Hala Shamsuddin MD
Statistical Review	Cheryl Dixon PhD
Product Quality Microbiology Review	Bryan Riley PhD; Steven Donald MS
Clinical Microbiology Review	Kerian Grande PhD
Clinical Pharmacology Review	Dakshina Chilukuri PhD
Division of Medication Error Prevention and Analysis	Aleksander Winiarski Pharm D
Office of Prescription Drug Promotion	Christine Corser Pharm D

1.0 Introduction

NDA 206110, Caspofungin Acetate for Injection, 50 mg/vial and 70 mg/vial submitted by Fresenius Kabi USA, LLC, provides for a new formulation of injectable caspofungin to be used for the treatment of the same indications as listed in the labeling for Cancidas[®] (caspofungin). This NDA was submitted as a 505(b)(2) application and the listed drug is Cancidas[®] (caspofungin) Injection, 50 mg/vial and 70 mg/vial, held by Merck (NDA 21227). Cancidas is approved for the treatment of adults and pediatric patients (3 months and older) for the following indications:

1. Empirical therapy for presumed fungal infections in febrile, neutropenic patients
2. Treatment of candidemia and the following *Candida* infections: intra-abdominal abscesses, peritonitis, and pleural space infections
3. Treatment of esophageal candidiasis
4. 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).

2.0 Background

The proposed drug product, Caspofungin Acetate for Injection, 50 mg/vial and 70 mg/vial is a new formulation of caspofungin for injection. The drug product differs from the listed drug in that it contains arginine and sodium hydroxide/hydrochloric acid whereas the listed drug formulation includes sucrose, mannitol and glacial acetic acid. The majority of the information submitted in the NDA relates to the chemistry, manufacturing and controls used in the manufacture of the proposed caspofungin drug product. The Applicant has requested a biowaiver for conducting in vivo bioequivalence studies on the basis of 21 CFR 320.22 (b).

The review team has completed their reviews of this application. For a detailed discussion of NDA 206110, please refer to discipline specific reviews and the Cross-Discipline Team Leader Review.

3.0 Product Quality

The Chemistry, Manufacturing and Controls (CMC) reviewer for this application is Lin Qi, PhD, and the product quality microbiology reviewers are Bryan Riley, PhD and Steven Donald, MS.

For drug substance information, reference is made to DMF (b) (4) held by (b) (4). A letter of authorization (LOA) was included in the NDA. The DMF was reviewed by Dr. Qi and found to be inadequate. The deficiencies were conveyed to the DMF holder.

The proposed drug product, Caspofungin Acetate for Injection, is a white to off-white cake or powder for intravenous infusion. In addition to the active ingredient, the 50 mg vial contains 100 mg of L-arginine, hydrochloric acid and sodium hydroxide and the 70 mg vial contains 140 mg of L-arginine, hydrochloric acid and sodium hydroxide. All excipients are of compendial grades, USP/NF. The drug product needs to be reconstituted with water and further diluted to achieve the target concentration of NMT 0.5 mg/mL using the recommended dilution agents.

Based on the stability information provided in the application, Dr. Qi has recommended that the proposed acceptance criteria in the proposed drug product specification for assay, water content, pH, and impurities be revised. These recommendations were conveyed to the Applicant.

Stability information provided for the drug product in the submission includes 12-month long-term and accelerated data for three representative batches of each product strength, 50 mg/vial and 70 mg/vial. The Applicant has proposed an expiration dating period of (b) (4) months at (b) (4). Based on the data submitted, Dr. Qi recommended that the drug product be stored refrigerated at 2° to 8°C (36° to 46°F), (b) (4) to the listed drug. This recommendation was conveyed to the Applicant and a response is pending.

The drug substance is manufactured by (b) (4). The drug product is manufactured at Fresenius Kabi USA, LLC at Grand Island, NY. In addition, several other facilities are involved in release and stability testing of the proposed drug product. An overall recommendation of withhold was made by the Office of Compliance for this NDA on October 21, 2014.

Dr. Qi concluded that insufficient information has been provided in the NDA to assure identity, strength, purity, and quality of the drug product and does not recommend approval from a CMC perspective. Dr. Riley and Mr. Donald recommend approval of the NDA from a product quality microbiology perspective.

4.0 Pharmacology/Toxicology

The pharmacology/toxicology reviewer for this application is Owen McMaster, PhD. No new nonclinical data were submitted in this NDA. Dr. McMaster concluded that there are no nonclinical data that would preclude approval. As arginine is commonly found in the diet and used at higher doses in other intravenous products, Dr. McMaster did not have any concerns about the presence of arginine in the proposed drug product. Dr. McMaster also recommended that the Applicant should reduce the acceptance limit for ‘any other single unspecified degradant’ to (b) (4)% and the limit on ‘total impurities’ to NMT (b) (4)%. These recommendations were conveyed to the Applicant on August 22, 2014.

5.0 Quality Biopharmaceutics

Houda Mahayni, PhD, is the Quality Biopharmaceutics reviewer for this application. The Applicant requested a waiver for conducting in vivo bioequivalence studies based on 21CFR 320.22(b). Dr. Mahayni concluded that the Applicant has provided adequate scientific justification to demonstrate that using L-arginine in the proposed drug product is not expected to alter the pharmacokinetics of caspofungin. Dr. Mahayni found the biowaiver request acceptable and recommends approval of the NDA.

6.0 Clinical Microbiology

Kerian Grande, PhD, is the clinical microbiology reviewer for this application. No new clinical microbiology information was submitted in this application. Dr. Grande's labeling recommendations have been incorporated into the Microbiology section of the package insert.

7.0 Clinical Pharmacology

Dakshina Chilukuri, PhD, is the clinical pharmacology reviewer for this application. Dr. Chilukuri notes that no new clinical pharmacology information was submitted in this NDA and that the application is acceptable from a clinical pharmacology perspective.

8.0 Clinical Efficacy/Safety

Hala Shamsuddin, MD, is the clinical reviewer for this application. No new clinical studies were submitted in this NDA. No new safety issues were identified in the literature. Dr. Shamsuddin concluded that the addition of L-arginine to the proposed drug product does not alter the risk/benefit assessment for caspofungin in the treatment of the approved indications. Dr. Shamsuddin recommends approval of the NDA.

Cheryl Dixon, PhD, is the statistics reviewer for this NDA. Dr. Dixon notes that as no new clinical studies were submitted by the Applicant, there are no statistical comments regarding the safety and efficacy of the product.

9.0 Labeling

Aleksander Winiarski, PharmD, from the Division of Medication Error Prevention and Analysis performed a labeling review. Dr. Winiarski's recommendations for labeling revisions have been incorporated. Christine Corser, Pharm D, from the Office of Prescription Drug Promotion provided labeling revisions that have been incorporated in labeling.

10.0 Pediatrics

Under the Pediatric Research and Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless the requirement is waived, deferred or inapplicable. As none of these criteria are applicable, this NDA is exempt from PREA requirements.

11.0 Other Regulatory Issues

The reference listed application, NDA 21227, Cancidas® (caspofungin) Injection, has the following unexpired patents listed in the Orange Book:

- US Patent No. 5,514,650 - Expiry Date: January 26, 2015
- US Patent No. 5,514,650*PED - Expiry Date: July 26, 2015
- US Patent No. 5,952,300 - Expiry Date: March 28, 2017
- US Patent No. 5,952,300*PED - Expiry Date: September 28, 2017
- US Patent No. 6,136,783 - Expiry Date: March 28, 2017
- US Patent No. 6,136,783*PED - Expiry Date: September 28, 2017

Fresenius Kabi USA, LLC has submitted Paragraph IV certification for the above patents in their NDA 505(b)(2) submission. On July 9, 2014, the Applicant notified the Agency that Paragraph IV certification notices were delivered to the listed drug patent and NDA holders on June 30, 2014. In an amendment dated August 14, 2014, the Applicant notified the Agency that Merck & Co. Inc. and Merck Sharp and Dohme Corp. have filed suit against Fresenius Kabi USA, LLC for patent infringement for patents 5,514,650 and 5,952,300.

This application was not presented to the Anti-Infective Drugs Advisory Committee (AIDAC), as there were no issues requiring input from the AIDAC.

12.0 Recommended Regulatory Action

I agree with the recommendations made by the review team that this NDA receive a Complete Response action due to the outstanding CMC issues listed below and the withhold status of the facilities.

1. During a recent inspection of the Fresenius Kabi USA, LLC, Grand Island, NY, manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.
2. Your application referenced the Drug Master File (DMF) (b) (4). This DMF was found inadequate to support your submission and a deficiency letter was sent to the DMF holder on September 23, 2014. These deficiencies must be adequately addressed before this application can be approved. As part of your response to this letter, include the date the DMF holder amended their DMF to address the deficiencies.



5. Stability data provided shows that the stability profile of the drug product is strongly temperature dependent. Therefore, the drug product should be stored at refrigerated condition. Revise the storage conditions to recommend storing the drug product at 2° to 8°C (36° to 46°F). In addition, revise the acceptance criteria for the tests noted below:
 - a. Any other individual unspecified impurity: NMT (b) (4)%
 - b. Total impurities: NMT (b) (4)%
 - c. Assay: (b) (4)% - (b) (4)%
 - d. Water content: NMT (b) (4)%

6. Regarding the analytical procedures (10-08-03-6723 and 10-08-03-6712) and methods validation provide the following:



7. Based on the pH results in the stability studies and the forced degradation results, revise the acceptance criteria for pH from (b) (4) to (b) (4) in the drug product specification.
8. Provide particulate matter testing results (USP <788>) for the infusion solutions of caspofungin acetate performed during the Large Volume Parenteral (LVP) Admixture Stability Study.

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/s/

SUMATHI NAMBIAR
10/21/2014