

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206110Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	(electronic stamp)
From	Dorota Matecka, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA #	206110
Applicant	Fresenius Kabi USA, LLC
Date of Submission	October 31, 2016 (<i>Class 1 NDA Resubmission</i>)
PDUFA Goal Date	December 31, 2016
Proprietary Name / 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
Recommended:	Approval

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

1. Introduction

This 505(b)(2) NDA submitted by Fresenius Kabi USA, LLC provides for a new injectable formulation of caspofungin acetate to be used for the same indications as specified in the labeling of the listed drug, Cancidas® (caspofungin acetate) for Injection, 50 mg/vial and 70 mg/vial (approved in 2001 via NDA 21227). The drug product proposed via the current NDA is a new formulation of caspofungin acetate powder for injection. Fresenius Kabi's caspofungin acetate for injection, 50 mg/vial and 70 mg/vial, differs from the listed drug in the excipients used in the formulation, i.e., the proposed drug product contains arginine and sodium hydroxide/hydrochloric acid whereas the listed drug formulation includes sucrose, mannitol and glacial acetic acid. In view of the similarities between the proposed and reference listed drugs, a biowaiver for conducting in-vivo bioequivalence studies was requested by the Applicant. The Applicant is relying on previous findings of efficacy and safety for Cancidas® for approval of the proposed drug product.

This NDA, originally submitted on December 27, 2013, was issued a Complete Response (CR) letter on October 21, 2014, due to several Product Quality deficiencies, which included the overall "Withhold" recommendation for manufacturing facilities and a deficient DMF referenced for the caspofungin acetate drug substance. These deficiencies were adequately addressed via the first (Class 2) NDA resubmission dated May 27, 2015. However, the NDA was again issued a CR letter on November 20, 2015 due to the pending patent issues. Most of

the reviewers found this NDA acceptable in the first review cycle, as described in their respective reviews of the original NDA and the previous CDTL reviews. The current (Class 1) NDA resubmission only contains minor updates to the labeling and labels, following labeling revisions recently approved for the listed drug, Cancidas®.

2. Background

Caspofungin acetate is a semisynthetic lipopeptide compound (echinocandin) synthesized from a fermentation product of *Glarea lozoyensis*. Caspofungin, an echinocandin, inhibits the synthesis of β (1,3)-D-glucan, an integral component of the cell wall of susceptible *Aspergillus* species and *Candida* species. Caspofungin has shown activity against *Candida* species and in regions of active cell growth of the hyphae of *Aspergillus fumigatus*.

3. Product Quality

The previous CMC review of NDA resubmission dated May 27, 2015 (review dated November 18, 2015 by Dorota Matecka, Ph.D.) recommended approval from the Product Quality perspective. The current NDA resubmission does not provide for any CMC changes; only minor, mainly formatting labeling revisions are proposed. In addition, the manufacturing facilities have been found in CGMP compliance as confirmed by the Office of Process and Facilities (on November 18, 2016, in Panorama).

Therefore, this NDA is recommended for approval from the Product Quality perspective (refer to the review by Dorota Matecka, Ph.D., entered into Panorama on December 19, 2016).

4. Nonclinical Pharmacology/Toxicology

Dr. Owen McMaster was the Pharmacology/Toxicology Reviewer for this application who concluded in the first cycle that there are no nonclinical data that would preclude the approval of this product (refer to the review dated September 25, 2014 in DARRTS). The same recommendation was made by Dr. McMaster for the current NDA resubmission (via review dated December 19, 2016, in DARRTS).

5. Clinical Pharmacology/Biopharmaceutics

Houda Mahayni, Ph.D., was the Biopharmaceutics Reviewer and Dakshina M. Chilukuri, Ph.D., was the Clinical Pharmacology Reviewer for this application. They both recommended an approval of this NDA in the first review cycle (refer to reviews dated September 17, 2014 and September 12, 2014, respectively, in DARRTS). In addition, the review of the current resubmission by Dr. Chilukuri confirms this recommendation (review dated December 12, 2016, in DARRTS).

6. Clinical Microbiology

Kerian Grande Roche, Ph.D, was the Clinical Microbiology Reviewer for this application and recommended approval with several minor labeling revisions (refer to the clinical microbiology review dated September 18, 2014 in DARRTS). No additional labeling recommendations were made for the current NDA resubmission (refer to the review dated December 16, 2016 in DARRTS).

7. Clinical/Statistical – Efficacy

The Clinical Reviewer, Dr. Hala Shamsuddin, concluded that since no new clinical studies were included in this NDA and no new safety information was presented or identified in the literature that would alter the favorable risk/benefit assessment of caspofungin in the treatment of the labeled indications, this NDA is recommended for approval from a clinical perspective (refer to reviews of the original NDA submission and the current resubmission by Dr. Shamsuddin in DARRTS dated October 2, 2014 and December 6, 2016, respectively).

Cheryl Dixon, Ph.D., was the Statistical Reviewer for this NDA and stated that no clinical studies were submitted by the Applicant in the current NDA and, therefore, there are no statistical comments regarding the safety and efficacy of the proposed drug product by Fresenius Kabi (via reviews of the original NDA and the current resubmission, dated September 17, 2014 and December 19, 2016, respectively, in DARRTS).

8. Safety

The applicant of the current 505(b)(2) NDA is relying on the previous findings of safety for the listed drug, Cancidas® (caspofungin acetate) for Injection. Dr. Shamsuddin concluded that no new safety information was presented or identified in the literature that would alter the favorable risk/benefit assessment of caspofungin in the treatment of the labeled indications (refer to reviews dated October 2, 2014, November 16, 2015, and December 6, 2016 in DARRTS).

9. Advisory Committee Meeting

There was no Advisory Committee Meeting for this application (the product is not an NME).

10. Pediatrics

The drug product proposed via this 505(b)(2) NDA does not contain a new active ingredient and is not a new dosage form. No new indication is proposed and no new dosing regimen is proposed. There is no new route of administration associated with the new product. For these reasons, the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), does not apply to this application. No pediatric studies will be required as a condition of approval.

11. Other Relevant Regulatory Issues

No clinical studies/trials were conducted in support of this NDA. Therefore, no inspection request was sent to the Office of Scientific Investigations (OSI).

There are several patents currently listed in the Orange Book for the listed drug application, NDA 21227 [Candida® (casprofungin acetate) for Injection, 50 mg/vial and 70 mg/vial]:

- 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

[It should be noted that, although Patent No. 5,514,650*PED is still listed in the Orange Book, it is now expired (as of July 26, 2015)].

Fresenius Kabi USA, LLC has submitted Paragraph IV certification for the above patents in their original NDA 505(b)(2) submission. Subsequently, the Applicant has submitted an NDA patent amendment (dated July 9, 2014) to certify that the Paragraph IV certification notices have been delivered to the listed drug patent and NDA holders (Merck & Co., Inc. and Merck Sharp & Dohme Corp.). In addition, in the 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. The expiration of the 30-month stay date is December 30, 2016, and, therefore, the Applicant is seeking final approval of the current NDA in anticipation of an outcome of the pending district court proceedings by expiry of the 30-month stay on December 30, 2016.

12. Labeling

The proposed labeling and labels for Casprofungin Acetate for Injection, 50 mg/vial and 70 mg/vial, were submitted in the NDA. No trade name was proposed for the drug product.

The Office of Prescription Drug Promotion (OPDP) had previously reviewed the proposed draft labeling and provided several comments (refer to the review dated September 11, 2014 in DARRTS). In addition, the Division of Medication Errors Prevention and Analysis (DMEPA) evaluated the proposed container and carton labels and package insert for areas of vulnerability that could lead to medication errors and provided several recommendations for the vial and

carton labels (refer to the reviews dated July 14, 2014, September 14, 2015, and December 13, 2016 in DARRTS).

The labeling recommendations from the review team were incorporated into the proposed package insert and container labels. Labeling will be identical to Cancidas® for the Indications, Contraindications, Warnings, Adverse Events, Drug-Drug Interactions, Use in Special Populations, Clinical Pharmacology, Toxicology, and Clinical Studies sections. The Dosage and Administration, Description and How Supplied sections were modified as needed to reflect the differences between this product and the listed drug.

13. Recommendations

I concur with the assessments made by the review team and recommend the issuance of an approval for this NDA (*by expiry of the 30-month stay on December 30, 2016*).

Dorota M.
Matecka -5

 Digitally signed by Dorota M. Matecka -5
DN: cn=Dorota M. Matecka -5, o=FDA, ou=People,
c=US, email=Dorota.M.Matecka@FDA.gov, ou=FDA, ou=People,
c=US, email=Dorota.M.Matecka@FDA.gov, ou=FDA, ou=People,
c=US, email=Dorota.M.Matecka@FDA.gov

Cross-Discipline Team Leader Review

Date	(electronic stamp)
From	Dorota Matecka, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA #	206110
Applicant	Fresenius Kabi USA, LLC
Date of Submission	October 31, 2016 (<i>Class 1 NDA Resubmission</i>)
PDUFA Goal Date	November 27, 2015
Proprietary Name / 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
Recommended:	<i>Approval</i>

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

1. Introduction

This 505(b)(2) NDA submitted by Fresenius Kabi USA, LLC provides for a new injectable formulation of caspofungin acetate to be used for the treatment of the same infections as specified in the labeling of the listed drug, Cancidas® (caspofungin acetate) for Injection, 50 mg/vial and 70 mg/vial (approved in 2001 via NDA 21227). The drug product proposed via current NDA is a new formulation of caspofungin acetate powder for injection. Fresenius Kabi's caspofungin acetate for injection, 50 mg/vial and 70 mg/vial, differs from the listed drug in the excipients used in the formulation, i.e., the proposed drug product contains arginine and sodium hydroxide/hydrochloric acid whereas the listed drug formulation includes sucrose, mannitol and glacial acetic acid. In view of the similarities between the proposed and reference listed drugs, a biowaiver for conducting in-vivo bioequivalence studies was requested by the Applicant. The Applicant is relying on previous findings of efficacy and safety for Cancidas® for approval of the proposed drug product.

This NDA, originally submitted on December 27, 2013, was issued a Complete Response (CR) letter on October 21, 2014, due to several Product Quality deficiencies, which included the overall "Withhold" recommendation for manufacturing facilities and a deficient DMF referenced for the caspofungin acetate drug substance. These deficiencies were adequately addressed via the first (Class 2) NDA resubmission dated May 27, 2015. However, the NDA was again issued a CR letter on November 20, 2015 due to the pending patent issues. Most of

the reviewers found this NDA acceptable in the first review cycle, as described in their respective reviews of the original NDA and the previous CDTL reviews. The current (Class 1) NDA resubmission only contains minor updates to the labeling and labels, following labeling revisions recently approved for the listed drug, Cancidas®.

2. Background

Caspofungin acetate is a semisynthetic lipopeptide compound (echinocandin) synthesized from a fermentation product of *Glarea lozoyensis*. Caspofungin, an echinocandin, inhibits the synthesis of β (1,3)-D-glucan, an integral component of the cell wall of susceptible *Aspergillus* species and *Candida* species. Caspofungin has shown activity against *Candida* species and in regions of active cell growth of the hyphae of *Aspergillus fumigatus*.

3. Product Quality

The previous CMC review of NDA resubmission dated May 27, 2015 (review dated November 18, 2015 by Dorota Matecka, Ph.D.) recommended approval from the Product Quality perspective. The current NDA resubmission does not provide for any CMC changes; only minor, mainly formatting labeling revisions are proposed. In addition, the manufacturing facilities have been found in CGMP compliance as confirmed by the Office of Process and Facilities (on November 18, 2016, in Panorama).

Therefore, this NDA is recommended for approval from the Product Quality perspective (refer to the review by Dorota Matecka, Ph.D., entered into Panorama on December 19, 2016).

4. Nonclinical Pharmacology/Toxicology

Dr. Owen McMaster was the Pharmacology/Toxicology Reviewer for this application who concluded in the first cycle that there are no nonclinical data that would preclude the approval of this product (refer to the review dated September 25, 2014 in DARRTS). The same recommendation was made by Dr. McMaster for the current NDA resubmission (via review dated December 19, 2016, in DARRTS).

5. Clinical Pharmacology/Biopharmaceutics

Houda Mahayni, Ph.D., was the Biopharmaceutics Reviewer and Dakshina M. Chilukuri, Ph.D., was the Clinical Pharmacology Reviewer for this application. They both recommended an approval of this NDA in the first review cycle (refer to reviews dated September 17, 2014 and September 12, 2014, respectively, in DARRTS). In addition, the review of the current resubmission by Dr. Chilukuri confirms this recommendation (review dated December 12, 2016, in DARRTS).

6. Clinical Microbiology

Kerian Grande Roche, Ph.D, was the Clinical Microbiology Reviewer for this application and recommended approval with several minor labeling revisions (refer to the clinical microbiology review dated September 18, 2014 in DARRTS). No additional labeling recommendations were made for the current NDA resubmission (refer to the review dated December 16, 2016 in DARRTS).

7. Clinical/Statistical – Efficacy

The Clinical Reviewer, Dr. Hala Shamsuddin, concluded that since no new clinical studies were included in this NDA and no new safety information was presented or identified in the literature that would alter the favorable risk/benefit assessment of caspofungin in the treatment of the labeled indications, this NDA is recommended for approval from a clinical perspective (refer to reviews of the original NDA submission and the current resubmission by Dr. Shamsuddin in DARRTS dated October 2, 2014 and December 6, 2016, respectively).

Cheryl Dixon, Ph.D., was the Statistical Reviewer for this NDA and stated that no clinical studies were submitted by the Applicant in the current NDA and, therefore, there are no statistical comments regarding the safety and efficacy of the proposed drug product by Fresenius Kabi (via reviews of the original NDA and the current resubmission, dated September 17, 2014 and December 19, 2016, respectively, in DARRTS).

8. Safety

The applicant of the current 505(b)(2) NDA is relying on the previous findings of safety for the listed drug, Cancidas® (caspofungin acetate) for Injection. Dr. Shamsuddin concluded that no new safety information was presented or identified in the literature that would alter the favorable risk/benefit assessment of caspofungin in the treatment of the labeled indications (refer to reviews dated October 2, 2014, November 16, 2015, and December 6, 2016 in DARRTS).

9. Advisory Committee Meeting

There was no Advisory Committee Meeting for this application (the product is not an NME).

10. Pediatrics

The drug product proposed via this 505(b)(2) NDA does not contain a new active ingredient and is not a new dosage form. No new indication is proposed and no new dosing regimen is proposed. There is no new route of administration associated with the new product. For these reasons, the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), does not apply to this application. No pediatric studies will be required as a condition of approval.

11. Other Relevant Regulatory Issues

No clinical studies/trials were conducted in support of this NDA. Therefore, no inspection request was sent to the Office of Scientific Investigations (OSI).

There are several patents currently listed in the Orange Book for the listed drug application, NDA 21227 [Candidas® (casposfungin acetate) for Injection, 50 mg/vial and 70 mg/vial]:

- 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

[It should be noted that, although Patent No. 5,514,650*PED is still listed in the Orange Book, it is now expired (as of July 26, 2015)].

Fresenius Kabi USA, LLC has submitted Paragraph IV certification for the above patents in their original NDA 505(b)(2) submission. Subsequently, the Applicant has submitted an NDA patent amendment (dated July 9, 2014) to certify that the Paragraph IV certification notices have been delivered to the listed drug patent and NDA holders (Merck & Co., Inc. and Merck Sharp & Dohme Corp.). In addition, in the 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. The expiration of the 30-month stay date is December 30, 2016, and, therefore, the Applicant is seeking final approval of the current NDA in anticipation of an outcome of the pending district court proceedings by expiry of the 30-month stay on December 30, 2016.

12. Labeling

The proposed labeling and labels for Casposfungin Acetate for Injection, 50 mg/vial and 70 mg/vial, were submitted in the NDA. No trade name was proposed for the drug product.

The Office of Prescription Drug Promotion (OPDP) had previously reviewed the proposed draft labeling and provided several comments (refer to the review dated September 11, 2014 in DARRTS). In addition, the Division of Medication Errors Prevention and Analysis (DMEPA) evaluated the proposed container and carton labels and package insert for areas of vulnerability that could lead to medication errors and provided several recommendations for the vial and

Cross-Discipline Team Leader Review

Date	(electronic stamp)
From	Dorota Matecka, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA #	206110
Applicant	Fresenius Kabi USA, LLC
Date of Submission	May 27, 2015 (<i>Class 2 NDA Resubmission</i>)
PDUFA Goal Date	November 27, 2015
Proprietary Name / 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
Recommended:	<i>Tentative Approval</i>

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

1. Introduction

This 505(b)(2) NDA submitted by Fresenius Kabi USA, LLC provides for a new injectable formulation of caspofungin acetate to be used for the treatment of the same infections as specified in the labeling of the listed drug, Cancidas® (caspofungin acetate) for Injection, 50 mg/vial and 70 mg/vial (approved in 2001 via NDA 21227). The drug product proposed via current NDA is a new formulation of caspofungin acetate powder for injection. Fresenius Kabi's caspofungin acetate for injection, 50 mg/vial and 70 mg/vial, differs from the listed drug in the excipients used in the formulation, i.e., the proposed drug product contains arginine and sodium hydroxide/hydrochloric acid whereas the listed drug formulation includes sucrose, mannitol and glacial acetic acid.

No clinical data have been submitted in this NDA as the applicant is relying on previous findings of efficacy and safety for Cancidas® for approval of this product. The majority of data submitted in the NDA relates to the chemistry, manufacturing and controls information for the proposed caspofungin acetate drug product. In view of the similarities between the proposed and listed drugs, a biowaiver for conducting in-vivo bioequivalence studies was requested by the applicant on the basis of 21 CFR 320.22 (b): "a drug product's in vivo bioavailability or bioequivalence may be considered self-evident".

This NDA, originally submitted on December 27, 2013, was issued a complete response (CR) letter on October 21, 2014, which listed several Product Quality deficiencies including the overall “Withhold” recommendation for manufacturing facilities from the Office of Compliance and a deficient DMF (b) (4) (referenced in the NDA for the caspofungin drug substance).

Most of the reviewers found this NDA acceptable in the first review cycle as described in their respective reviews of the original NDA and the first CDTL review dated October 16, 2014. The current CTDL review covers only the reviews of the Applicant’s response to the deficiencies outlined in the CR letter.

2. Background

Caspofungin acetate is a semisynthetic lipopeptide compound (echinocandin) synthesized from a fermentation product of *Glarea lozoyensis*. Caspofungin, an echinocandin, inhibits the synthesis of β (1,3)-D-glucan, an integral component of the cell wall of susceptible *Aspergillus* species and *Candida* species. Caspofungin has shown activity against *Candida* species and in regions of active cell growth of the hyphae of *Aspergillus fumigatus*.

As stated above, Cancidas[®] (caspofungin acetate) for Injection was approved via NDA 21227 in 2001. There are no other caspofungin drug products approved for use in humans in the US at this time. The caspofungin acetate drug product proposed by Fresenius Kabi, USA, LLC has the same drug substance, dosage form, concentration, route of administration, and indications as Cancidas[®]. Due to the difference in the formulation (i.e., a change in the excipients not permitted per 314.94(a)(9)(iii)), this application was submitted as 505(b)(2) application and not as a 505(j) application.

3. Product Quality Microbiology/CMC

The Product Quality Microbiology Reviewers were Steven P. Donald, M.S. and Bryan S. Riley, Ph.D. who recommended this NDA for approval from the product quality microbiology standpoint in the first review cycle (review dated August 8, 2014 in DARRTS).

The CMC Reviewer of the original NDA was Lin Qi, Ph.D. who recommended a non-approval based on several outstanding product quality deficiencies including the overall “Withhold” recommendation for manufacturing facilities from the Office of Compliance and a deficient DMF (b) (4) referenced in the NDA for the caspofungin drug substance (refer to CMC review dated October 21, 2014 in DARRTS). The product quality deficiencies listed in the CR letter for the original NDA have been addressed in the current NDA resubmission dated May 27, 2015, which was reviewed by Dorota Matecka, Ph.D. who concluded that the following Product Quality deficiencies listed in the CR letter have been resolved satisfactorily:

- All facilities, including the drug product manufacturing facility, Fresenius Kabi USA, LLC, Grand Island, NY, were evaluated and found acceptable by the Office of Process and Facilities for this NDA.
- The responses to DMF (b) (4) deficiencies forwarded to the DMF holder on September 23, 2014, have been reviewed and found acceptable. Per CMC Review # 2 dated November 13, 2015 in DARRTS, this DMF is now considered adequate to support this NDA.
- (b) (4)
- Several acceptance criteria for drug product quality attributes have been revised and the drug product specification has been found acceptable.
- The requested results of the particulate matter testing per USP <788> for the infusion solutions of caspofungin acetate performed during the Large Volume Parenteral (LVP) Admixture Stability Study have been provided in the resubmission and were found acceptable.
- The proposed room temperature storage conditions and the expiration dating of 24 months have been found acceptable for the proposed drug product based on the assessment of the overall information submitted for the proposed drug product in the NDA, including the 24-month stability data for the three registration batches of the drug product (both strengths) stored at the long term conditions (25°C ± 2°C/60% ± 5% RH) provided in the current NDA resubmission.

Based on the above findings, this NDA is now recommended for approval from the CMC perspective (refer to the review by Dorota Matecka, Ph.D., entered into Panorama on November 18, 2015).

4. Nonclinical Pharmacology/Toxicology

Dr. Owen McMaster was the Pharmacology/Toxicology Reviewer for this application who concluded in the first cycle that there are no nonclinical data that would preclude the approval of this product (refer to the review dated September 25, 2014 in DARRTS).

5. Clinical Pharmacology/Biopharmaceutics

Houda Mahayni, Ph.D., was the Biopharmaceutics Reviewer and Dakshina M. Chilukuri, Ph.D., was the Clinical Pharmacology Reviewer for this application. They both recommended an approval of this NDA in the first review cycle (refer to reviews dated September 17, 2014 and September 12, 2014, respectively, in DARRTS). No new reviews were conducted for this NDA resubmission.

6. Clinical Microbiology

Kerian Grande Roche, Ph.D, was the Clinical Microbiology Reviewer for this application (refer to the first cycle review microbiology dated review dated September 18, 2014 in DARRTS). No new review was filed for this NDA resubmission.

7. Clinical/Statistical – Efficacy

Hala Shamsuddin, MD, who was the Clinical Reviewer concluded that since no new clinical studies were included in this NDA and no new safety information was presented or identified in the literature that would alter the favorable risk/benefit assessment of caspofungin in the treatment of the labeled indications, this NDA is recommended for approval from a clinical perspective (refer to reviews of the original NDA submission and the current resubmission by Dr. Shamsuddin in DARRTS dated October 2, 2014 and November 16, 2015, respectively).

Cheryl Dixon, Ph.D., was the Statistical Reviewer for this NDA and stated that no clinical studies were submitted by the Applicant in the current NDA and, therefore, there are no statistical comments regarding the safety and efficacy of the proposed drug product by Fresenius Kabi (review dated September 17, 2014 in DARRTS). No new statistical review was filed for the current resubmission.

8. Safety

The applicant of the current 505(b)(2) NDA is relying on the previous findings of safety for the listed drug, Cancidas® (caspofungin acetate) for Injection. Dr. Shamsuddin concluded that no new safety information was presented or identified in the literature that would alter the favorable risk/benefit assessment of caspofungin in the treatment of the labeled indications (refer to reviews dated October 2, 2014 and November 16, 2015 in DARRTS).

9. Advisory Committee Meeting

There was no Advisory Committee Meeting for this application (the product is not an NME).

10. Pediatrics

The drug product proposed via this 505(b)(2) NDA does not contain a new active ingredient and is not a new dosage form. No new indication is proposed and no new dosing regimen is proposed. There is no new route of administration associated with the new product. For these reasons, the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), does not apply to this application. No pediatric studies will be required as a condition of approval.

11. Other Relevant Regulatory Issues

No clinical studies/trials were conducted in support of this NDA. Therefore, no inspection request was sent to the Office of Scientific Investigations (OSI).

There are several patents listed in the Orange Book for the listed drug application, NDA 21227 [Candidas® (caspofungin acetate) for Injection, 50 mg/vial and 70 mg/vial]. They include two patents: No. 5,378,804 and 5,792,746, which expired on September 16, 2013, and for which the Applicant of the current NDA, Fresenius Kabi USA, LLC, submitted Paragraph II certification.

At the time of the original NDA 206110 submission (on December 27, 2013) the following unexpired patents were listed in the Orange Book for NDA 21227:

- 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 original NDA 505(b)(2) submission. Subsequently, the Applicant has submitted an NDA patent amendment (dated July 9, 2014) to certify that the Paragraph IV certification notices have been delivered to the listed drug patent and NDA holders (Merck & Co., Inc. and Merck Sharp & Dohme Corp.). In addition, in the 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.

On November 13, 2014, the Applicant submitted a Patent Amendment to convert the Paragraph IV to a Paragraph III certification for Patent No. 5,514,650. It should be noted that, although this patent is still listed in the Orange Book, it is now expired (as of July 26, 2015). The other patents, which are currently pending for Candidas® are listed above.

12. Labeling

The proposed labeling and labels for Caspofungin Acetate for Injection, 50 mg/vial and 70 mg/vial, were submitted in the NDA. No trade name was proposed for the drug product.

The Office of Prescription Drug Promotion (OPDP) has reviewed the proposed draft labeling and provided several comments (refer to the review dated September 11, 2014 in DARRTS).

In addition, the Division of Medication Errors Prevention and Analysis (DMEPA) evaluated the proposed container and carton labels and package insert for areas of vulnerability that could lead to medication errors and provided several recommendations for the vial and carton labels (refer to the reviews dated July 14, 2014 and September 14, 2015 in DARRTS).

The labeling recommendations from the review team were incorporated into the proposed package insert and container labels. Labeling will be identical to Cancidas® for the Indications, Contraindications, Warnings, Adverse Events, Drug-Drug Interactions, Use in Special Populations, Clinical Pharmacology, Toxicology, and Clinical Studies sections. The Dosage and Administration, Description and How Supplied sections were modified as needed to reflect the differences between this product and the listed drug.

13. Recommendations

I concur with the assessments made by the review team and recommend the issuance of an approval for this NDA. However, due to the unexpired patents for Cancidas®, a tentative approval is recommended at the present time.

Dorota M.
Matecka -S

Digitally signed by Dorota M. Matecka -S
DN: cn=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=FDA, o.2.24.2.19200000.000.1.1=1309122391,
cn=Dorota M. Matecka -S
Date: 2015.11.18 13:28:31 -0500