CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206110Orig1s000

MEDICAL REVIEW(S)

Clinical Memo

NDA	206110 SDN 0019
Applicant	Fresenius Kabi
Date of Submission	October 31, 2016
PDUFA Goal Date	December 31, 2016
Established Name	Caspofungin acetate
Reference Licensed Drug	Cancidas® (Merck)
Dosage forms / Strength	50 mg and 70 mg vials for injection
Proposed Indication(s)	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
Reviewer/Team Leader	Hala Shamsuddin MD
Recommendation	Approval

This NDA submission was recommended for approval from a clinical standpoint (review filed in DARRTS). As no clinical studies were performed in support of this 505(b)(2) submission that relied on the FDA's previous findings of safety and efficacy for the reference listed drug Cancidas® (NDA 21227), financial disclosures are not applicable and were not submitted by the Applicant.

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

/s/

HALA H SHAMSUDDIN
12/21/2016

Clinical Review

NDA	206110 SDN 0019
Applicant	Fresenius Kabi
Date of Submission	October 31, 2016
PDUFA Goal Date	December 31, 2016
Established Name	Caspofungin acetate
Reference Licensed Drug	Cancidas® (Merck)
Dosage forms / Strength	50 mg and 70 mg vials for injection
Proposed Indication(s)	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
Reviewer/Team Leader	Hala Shamsuddin MD
Recommendation	Approval

Introduction and Background

Caspofungin (Cancidas®, Merck) is an echinocandin antifungal drug that was approved in 2001 (NDA 21227). It is indicated in adults and pediatric patients 3 months or older for:

- Empirical therapy for presumed fungal infections in febrile, neutropenic patients (granted 2004)
- Treatment of candidemia and the following *Candida* infections: intra-abdominal abscesses, peritonitis, and pleural space infections (granted 2003)
- Treatment of esophageal candidiasis (granted 2002)
- Treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies (granted 2001)

Cancidas is marketed as lyophilized vials containing 50 mg or 70 mg caspofungin. The recommended dose in adults ≥ 18 years of age is 70 mg loading dose followed by 50 mg once daily. In patients 3 months of age to 17 years of age, the dose is 70 mg/m^2 loading followed by 50 mg/m^2 once daily, not to exceed 70 mg daily.

On December 27, 2013, the Applicant submitted NDA 206110 seeking approval of caspofungin acetate for the same indications as the approved reference licensed drug (RLD) product Cancidas® under section 505(b)(2) of the FD&C act, relying on the Agency's findings of efficacy and safety for the RLD to support approval. Similar to the RLD, caspofungin acetate will be supplied in lyophilized 50 mg and 70 mg vials. Similar to the RLD, each 50 mg vial contains 54.6 mg caspofungin, but the 70 mg vial contains 77.2 mg, compared to (b) (4) mg in Cancidas. This new formulation also differs from Cancidas in that the 50 mg vial of

Reference ID: 4023162

contains 100 mg arginine and the 70 mg vial contains 140 mg arginine whereas Cancidas contains sucrose and mannitol. No new toxicology, pharmacology, microbiology or clinical studies were submitted. And the Applicant was granted a waiver for conducting in vivo bioequivalence studies as per 21CFR 320.22 (b). The CMC reviewer did not recommend approval because insufficient information was provided to assure identity, strength, purity and quality of the drug product. Additionally, the manufacturing facilities for the drug substance and the drug product failed inspections and a recommendation of withhold was made by the Office of Compliance in October 2014. All other disciplines recommended approval. A Complete Response was issued detailing the deficiencies on October 21, 2014.

The Applicant submitted a Quality Information Amendment for review on May 27, 2015 that adequately addressed the manufacturing deficiencies. Tentative Approval was granted on November 20, 2015 due to pending litigation related to patent infringement that was filed against the Applicant by the innovator Merck Sharp &Dohme Corp. on August 7, 2014. The expiration of the 30 month stay is December 30, 2016. 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.

Review and Recommendations:

From a clinical standpoint, this NDA was recommended for approval during the initial submission. No new clinical information was submitted to alter the previous recommendation of approval. Labeling was updated to be identical to Cancidas® labeling 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 and Chemistry and Manufacturing sections were be modified to reflect the differences between this product and the RLD.

Reference ID: 4023162

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

/s/

HALA H SHAMSUDDIN
12/06/2016

Clinical Review

NDA	206110 SDN 0013
Applicant	Fresenius Kabi
Date of Submission	May 27, 2015
PDUFA Goal Date	November 27, 2015
Established Name	Caspofungin acetate
Reference Licensed Drug	Cancidas® (Merck)
Dosage forms / Strength	50 mg and 70 mg vials for injection
Proposed Indication(s)	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
Reviewer/Team Leader	Hala Shamsuddin MD
Recommendation	Approval

Introduction and Background

Caspofungin (Cancidas®, Merck) is an echinocandin antifungal drug that was approved in 2001 (NDA 21227). It is indicated in adults and pediatric patients 3 months or older for:

- Empirical therapy for presumed fungal infections in febrile, neutropenic patients (granted 2004)
- Treatment of candidemia and the following *Candida* infections: intra-abdominal abscesses, peritonitis, and pleural space infections (granted 2003)
- Treatment of esophageal candidiasis (granted 2002)
- Treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies (granted 2001)

Cancidas is marketed as lyophilized vials containing 50 mg or 70 mg caspofungin. The recommended dose in adults ≥ 18 years of age is 70 mg loading dose followed by 50 mg once daily. In patients 3 months of age to 17 years of age, the dose is 70 mg/m^2 loading followed by 50 mg/m^2 once daily, not to exceed 70 mg daily.

On December 27, 2013, the applicant submitted NDA 206110 seeking approval of caspofungin acetate for the same indications as the approved reference licensed drug (RLD) product Cancidas® under section 505(b)(2) of the FD&C act, relying on the Agency's findings of efficacy and safety for the RLD to support approval. Similar to the RLD, caspofungin acetate will be supplied in lyophilized 50 mg and 70 mg vials. Similar to the RLD, each 50 mg vial contains 54.6 mg caspofungin, but the 70 mg vial contains 77.2 mg, compared to (b) (4) mg in Cancidas. This new formulation also differs from Cancidas in that the 50 mg vial of contains 100 mg arginine and the 70 mg vial contains 140 mg arginine whereas Cancidas

Reference ID: 3847454

contains sucrose and mannitol. The applicant was granted a waiver for conducting in vivo bioequivalence studies based on 21CFR 320.22 (b). No new toxicology, pharmacology, microbiology or clinical studies were submitted. The CMC reviewer did not recommend approval because insufficient information was provided to assure identity, strength, purity and quality of the drug product. Additionally, the manufacturing facilities for the drug substance and the drug product failed inspections and a recommendation of withhold was made by the Office of Compliance in October 2014. All other disciplines recommended approval. A Complete Response was issued to the applicant on October 21, 2014.

The applicant is now submitting a Quality Information Amendment for review.

Review and Recommendations:
No new clinical information was submitted to alter the previous recommendation of approval. 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 and Chemistry and Manufacturing sections will be modified as needed to reflect the differences between this product and the RLD.

Reference ID: 3847454

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

/s/

HALA H SHAMSUDDIN
11/16/2015

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	December 27, 2013
PDUFA Goal Date	October 27, 2014
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)	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
Recommended:	Complete Response

** 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 listed in the listed drug labeling. The listed drug for this 505(b)(2) NDA is Cancidas® (caspofungin acetate) for Injection, 50 mg/vial and 70 mg/vial, approved in 2001 via NDA 21227. The drug product proposed via this 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.

There is no IND associated with the application and no clinical data have been submitted. The applicant is relying on previous findings of efficacy and safety for Cancidas® for approval of this product. The majority of the submitted information submitted in the NDA relates to the chemistry, manufacturing and controls used in the manufacture of 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".

Reference ID: 3644620

2. Background

Caspofungin acetate 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. CMC/Device

The CMC Reviewer was Lin Qi, Ph.D., and the Product Quality Microbiology Reviewers were Steven P. Donald, M.S. and Bryan S. Riley, Ph.D. Their findings are summarized below.

Caspofungin acetate drug substance is manufactured by (b) (4) For all 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 inadequate to support the current NDA with several deficiencies identified and conveyed to the DMF holder. A response to these deficiencies is currently pending.

The proposed drug product, Caspofungin Acetate for Injection, is a white to off-white cake or powder for intravenous infusion available in two strengths, 50 mg/vial or 70 mg/vial. In addition to the active ingredient, the 50 mg vial contains 100 mg of L-arginine, hydrochloric acid and sodium hydroxide whereas the 70 mg vial contains 140 mg of L-arginine, hydrochloric acid and sodium hydroxide. All excipients are of the compendial grades, USP/NF. The drug product needs to be reconstituted with water and further diluted into the infusion bags to achieve the target concentration of NMT 0.5 mg/mL using the dilution agents recommended in the package insert. The stability information submitted in support of the recommended storage conditions and holding time for the infusion solutions did not include the results of USP <788> test for particulate matter. This information was requested from the Applicant and a response is pending.

(b) (4)

Reference ID: 3644620

(b) (4)

The drug product specification includes tests for description, reconstitution time, constitution solution tests per USP <1> (completeness, clarity, visual color, visible particles), pH, water content, uniformity of dosage units, instrumental color, identification, (b) (4), assay, impurities, particle contamination (USP <788>), osmolality, bacterial endotoxins, sterility, and statement of compliance per USP <467>. 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 tightened. These recommendations were conveyed to the Applicant; however, they have not been yet addressed.

As mentioned above, the proposed drug product manufacturing process includes a (b) (4) . These aspects of the manufacturing process, as well as integrity of the container closure system, and the proposed microbiological quality attributes in the drug product specification were evaluated by the Product Quality Microbiology Reviewers, Mr. Steven Donald and Dr. Bryan Riley who recommended this NDA for approval from the product quality microbiology standpoint (review dated August 8, 2014 in DARRTS).

The drug product will be filled into (b) (4), Type I USP glass vials (10 mL, 20 mm), with (b) (4) rubber stoppers (20 mm) and aluminum crimped flip cap seals. Stability information provided for the drug product in the submission includes 12-month of long term and accelerated data for three representative batches of each product strength, 50 mg/vial and 70 mg/vial and an expiration dating period of (b) (4) months at (b) (4) has been proposed by the Applicant. However, based on the review of the product information available in the NDA, including the stability data, 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; however, it has not been yet addressed.

The drug product is manufactured at Fresenius Kabi USA, LLC at Grand Island, NY. In addition, several other facilities will be involved in release and stability testing of the proposed drug product. The list of all facilities is included in the CMC review. An overall recommendation has not yet been issued by the Office of Compliance for this NDA; however, it should be noted that the status of the Fresenius Kabi drug product manufacturing facility is currently indicated as OAI in the EES system.

Dr. Qi concluded that insufficient information has been provided in the current NDA to assure identity, strength, purity, and quality of the drug product and, therefore, this NDA is not recommended for approval from a CMC perspective (for details and a list of deficiencies refer to the CMC review dated September 19, 2014 in DARRTS).

Reference ID: 3644620

4. Nonclinical Pharmacology/Toxicology

Dr. Owen McMaster was the Pharmacology/Toxicology Reviewer for this application.

No pharmacology or pharmacokinetics or ADME or toxicokinetics or toxicology studies were submitted for review since the Applicant intends to rely on the Agency's findings of safety and efficacy for Cancidas, and on the nonclinical information provided in the approved Cancidas® labeling. Dr. McMaster has no concerns regarding the use of arginine in the proposed caspofungin acetate formulation as arginine is commonly found in the diet and is used in much higher doses in other intravenous preparations. Dr. McMaster also commented on the issue of impurities stating that the Applicant should follow the recommendations of the ICH Q3B(R2) Guidance and revise the proposed acceptance limit for "Any Other Unspecified Degradation Product" and "Total Impurities" to NMT (b) (4) % and NMT (b) (4) %, respectively. Dr. McMaster noted that these recommendations were conveyed to the Applicant in an IR letter on August 22, 2014 (per CMC review by Dr. Lin Qi).

Based on the above evaluation, Dr. McMaster concluded that there are no nonclinical data that would preclude the approval of this product. However, he recommended that the Applicant revise the limits on acceptance criteria for impurities, as described above (for details 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. Their findings and recommendations are summarized below.

This NDA includes a bioequivalence (BE) waiver request for the proposed drug product (referring to the listed drug, Cancidas®, approved under NDA 21227). The focus of the biopharmaceutics review is on the evaluation and acceptability of the data supporting the approval of the BE waiver request.

Dr. Mahayni noted in her review that the proposed product formulation differs from the listed drug (Cancidas®) in a (b) (4); i.e., the proposed product formulation contains L-arginine whereas the listed drug contains sucrose and mannitol. Per Dr. Mahayni's request, the Applicant has provided a scientific justification that the substitution of L-arginine for sucrose and mannitol will not affect the systemic exposure, the pharmacologic activity, or the safety of caspofungin. In addition, at a request of Dr. Mahayni, the Applicant has also provided results of the comparative pH and osmolarity testing for the proposed drug product and the listed drug. These results were found comparable with pH and osmolarity data slightly lower for the drug product versus the listed drug. In Dr. Mahayni's assessment, the small differences in these attributes between the proposed and the listed drugs are considered within the range of normal physiological system and, therefore, insignificant. Dr. Mahayni concluded that based on the overall information for the pH, osmolality, and pharmacological activity of L-arginine,

Reference ID: 3644620

there is adequate scientific evidence supporting the approval of the in vivo BA/BE waiver request. Therefore, the biowaiver is granted and this NDA is recommended for approval from the biopharmaceutics perspective (review dated September 17, 2014 in DARRTS).

The Clinical Pharmacology Reviewer, Dr. Chilukuri, stated that since no new clinical pharmacology data were submitted by the Applicant, the clinical pharmacology team has no comments and recommends an approval of this 505(b)(2) NDA. In addition, the labeling submitted by the applicant contained no new changes to the clinical pharmacology section (review dated September 12, 2014 in DARRTS).

6. Clinical Microbiology

Kerian Grande Roche, Ph.D, was the Clinical Microbiology Reviewer for this application.

No new clinical microbiology information was submitted in this application; however, the labeling for the proposed drug product was submitted and reviewed. Dr. Roche concluded that the clinical microbiology subsection (12.4) and references (15.0) of the Applicant's proposed labeling for caspofungin acetate for injection are in agreement with those sections in the labeling for the listed drug; therefore, only minor formatting corrections have been recommended (refer to the microbiology dated review dated September 18, 2014 in DARRTS).

7. Clinical/Statistical – Efficacy

Hala Shamsuddin, MD, was the Clinical Reviewer, and Cheryl Dixon, Ph.D., was the Statistical Reviewer for this NDA.

The Clinical Reviewer stated that this 505(b)(2) NDA, which provides for a new intravenous formulation of caspofungin acetate, does not contain any nonclinical or clinical studies as 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. The Applicant has submitted the safety summary from 1951 individuals that is included in the Cancidas® labeling. In addition, a PubMed search performed by both, the Applicant and the Clinical Reviewer, did not identify any new safety information that was not already included in the listed drug labeling. The clinical review includes evaluation of the use of L-arginine in the proposed formulation of caspofungin acetate. Based on the information from literature and for FDA-approved drug products containing L-arginine, Dr. Shamsuddin concluded that the exposure to L-arginine resulting from this caspofungin preparation is lower than the exposure resulting from average dietary intake and similar to exposures from the administration of at least one approved product for the treatment of pulmonary artery hypertension, and, therefore, the addition of L-arginine to this caspofungin preparation does not alter the favorable risk/benefit assessment of caspofungin in the treatment of the approved indications.

Reference ID: 3644620

Dr. Shamsuddin concluded that since no new clinical studies were included in this NDA submission 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 review dated October 2, 2014 in DARRTS).

Dr. Dixon 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. In addition, since the Applicant is relying on the listed drug approved labeling, no changes to the adverse reactions and clinical studies sections are recommended (review dated September 17, 2014 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. As described above, 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. As stated in the clinical review, the annual Periodic Safety Reports (PSUR) submitted for Cancidas® were reviewed. Labeling updates pertaining to AEs included the addition of the term “angioedema” in the post-marketing section in 2010, and moving Hypersensitivity reactions from the Adverse Reactions section to the Warnings and Precautions section in 2012 to harmonize echinocandin labeling. Cancidas® labeling was last updated in August 2013 with changes not pertaining to safety (refer to review dated October 2, 2014 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.

Reference ID: 3644620

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 [Cancidas® (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.

In addition, there are following unexpired patents 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 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.

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 review dated July 14, 2014 in DARRTS).

The labeling recommendations from the review team were incorporated into the proposed package insert and container labels and conveyed to the Applicant. The labeling review and negotiations are presently ongoing.

Reference ID: 3644620

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

  I concur with the assessments made by the review team and recommend the issuance of a Complete Response for this NDA.

- Risk Benefit Assessment

  The risk-benefit assessment for this application focused on significant cGMP and CMC issues identified during the review cycle:

  - *The CGMP status of the drug product manufacturing facility is not acceptable.*

  - *DMF* (b) (4) *referenced for caspofungin acetate to support this NDA is deficient.*

  - *Several deficiencies and comments regarding the drug product manufacturing process and controls, which were conveyed to the Applicant on August 22, 2014 and September 22, 2014, remain outstanding.*

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

  Not applicable

- Recommendation for other Postmarketing Study Commitments

  Not applicable

- Recommended Comments to Applicant

  The following deficiencies should be included in the Complete Response letter (*items 3-8 have been previously communicated to the Applicant*):

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. *DMF* (b) (4) *referenced for caspofungin acetate drug substance to support this NDA is deficient.*

(b) (4)

Reference ID: 3644620

(b) (4)

5. *Stability data provided shows that the stability profile of the drug product is strongly temperature dependent. Therefore, we recommend that the drug product be stored at refrigerated condition. In addition, we recommended that the acceptance criteria for the following tests be revised as follows:*

    - *Any other individual unspecified impurity: NMT* (b) (4) *%*
    - *Total impurities: NMT* (b) (4) *%*
    - *Assay:* (b) (4) *% -* (b) (4) *%*
    - *Water content: NMT* (b) (4) *%*

    Update the NDA with the revised specifications and labeling.

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

(b) (4)

7. *Based on the pH results in the stability studies and the forced degradation results, it is recommended that the acceptance criteria for pH be revised from* (b) (4) *to* (b) (4) (b) (4) *in the drug product specification.*

8. *The particulate matter (USP<788>) test results were not found in the "Large Volume Parenteral (LVP) Admixture Stability Study Report". Please provide particulate matter testing results (USP <788>) performed during the Large Volume Parenteral (LVP) Admixture Stability Study.*

Reference ID: 3644620

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

/s/

DOROTA M MATECKA
10/16/2014

Clinical Review

NDA	206110 SDN 000
Applicant	Fresenius Kabi
Date of Submission	December 27, 2013
PDUFA Goal Date	October 26, 2014
Established Name	Caspofungin acetate
Reference Licensed Drug	Cancidas® (Merck)
Dosage forms / Strength	50 mg and 70 mg vials for injection
Proposed Indication(s)	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
Reviewer	Hala Shamsuddin MD
Team Leader	Thomas Smith MD
Recommendation	Approval

Introduction

The applicant is seeking approval of caspofungin acetate for the same indications as the approved reference licensed drug (RLD) product Cancidas® under section 505(b)(2) of the FD&C act. The applicant's formulation substitutes L-arginine for the sucrose and mannitol in Cancidas. The applicant contends that this substitution does not alter the pharmacokinetics, pharmacodynamics, safety or efficacy of the drug product and intends to rely on the Agency's findings of efficacy and safety for the RLD to support approval.

Background

Caspofungin (Cancidas®, Merck) is an echinocandin antifungal drug that was approved in 2001 (NDA 21227). It is indicated in adults and pediatric patients 3 months or older for:

- Empirical therapy for presumed fungal infections in febrile, neutropenic patients (granted 2004)
- Treatment of candidemia and the following *Candida* infections: intra-abdominal abscesses, peritonitis, and pleural space infections (granted 2003)
- Treatment of esophageal candidiasis (granted 2002)
- Treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies (granted 2001)

Cancidas is marketed as lyophilized vials containing 50 mg or 70 mg caspofungin. The recommended dose in adults ≥ 18 years of age is 70 mg loading dose followed by 50 mg once

Reference ID: 3631442

daily. In patients 3 months of age to 17 years of age, the dose is 70 mg/m^2 loading followed by 50 mg/m^2 once daily, not to exceed 70 mg daily[1].

CMC

Similar to the RLD, caspofungin will be supplied in lyophilized vials. Each 50 mg vial contains 54.6 mg caspofungin (similar to Cancidas), while the 70 mg vial contains 77.2 mg (compared to (b) (4) mg in Cancidas). The 50 mg vial contains 100 mg arginine and the 70 mg vial contains 140 mg arginine.

The CMC reviewer, Lin Qi, recommended against approval. The DMF file for the drug substance was found to be inadequate to support the application. In addition, the manufacturing facility failed inspections.

Nonclinical Pharmacology/Toxicology

No non-clinical studies were conducted for this application. No additional Pharmacology/toxicology data were included in the application other than described in the approved RLD product labeling.

Clinical Pharmacology

No new pharmacology information was included in the application other than described in the approved RLD product labeling.

Clinical Microbiology

No new clinical microbiology information was included in the application other than described in the approved RLD product labeling.

Clinical/Statistical- Efficacy

No clinical studies were conducted in support of this application. The clinical studies conducted in support of efficacy of Cancidas for the approved indications are detailed in the approved RLD product labeling.

Safety

No clinical studies were conducted in support of this application.

Cancidas

The applicant submitted the safety summary from 1951 individuals that is included in Cancidas labeling. The applicant also performed a PubMed search on May 7, 2013 using the terms “caspofungin AND (safety OR efficacy)” and identified 268 publications, of which 2

[1] http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021227s030lbl.pdf

Reference ID: 3631442

studies were cited. In the study by Cornely et al.[2] caspofungin doses of 70, 100, 150 or 200 once daily were used as first line therapy for invasive aspergillosis in a total of 46 patients. The median duration of exposure was 24.5 days. No dose limiting toxicities were noted. The overall mortality at 12 weeks was 28.3%. 42 SAEs occurred in 26 patients, none was assessed as drug related. In the study by Kohno et al[3], caspofungin was compared to micafungin in the treatment of 120 patients with invasive candidiasis, esophageal candidiasis and aspergillosis. SAEs were not noted in the caspofungin recipients. Nine caspofungin patients and 10 micafungin patients died. None of the deaths was assessed as drug related.

Reviewer's Comments

In 2008, Merck submitted NDA efficacy supplement that included the results of a clinical trial evaluating the efficacy of Cancidas 150 mg once daily compared to 50 mg once daily in the treatment of patients with invasive candidiasis. The overall safety profile (AEs and SAEs) of the 150 mg dose was similar to the safety profile of the 50 mg dose. Mortality at the end of the study was approximately 34% in the 50 mg arm and 38% in the 150 arm. A higher percentage of patients died during the first 10 days of therapy (17% vs. 12%) or by the end of caspofungin therapy (21% vs. 14%) in the 150 mg arm compared to the 50 mg arm. The higher percentage of deaths in the 150 mg arm mainly occurred in males less than 65 years of age and was unexplained. The reviewer and the sponsor assessed all the deaths as unrelated to the drug, and attributed the deaths to the underlying disease (Review in DARRTS, NDA 21-227/S023).

A PubMed search was conducted on April 14, 2014 using the term "caspofungin" and was limited to 2008-2014 time period. The search identified 1045 articles in the English Language. Further limiting the search to "clinical trials" identified 61 publications, of which 18 reported efficacy and/or safety of caspofungin in the treatment of invasive candidiasis, as first-line or salvage therapy for invasive aspergillosis or as empirical therapy for invasive fungal infections in patients with febrile neutropenia. These publications included the two trials cited by the applicant. Some of the trials used doses higher than the approved 50 mg daily dose (70, 100 or 150 mg). Overall, review of these publications did not identify any new safety information that was not already included in the RLD product labeling (See Appendix 1 for literature citations).

The annual Periodic Safety Reports (PSUR) submitted for Cancidas were also reviewed. Labeling updates pertaining to AEs included the addition of the term "angioedema" in the post-marketing section in 2010, and moving Hypersensitivity reactions from the Adverse Reactions section to the Warnings and Precautions section in 2012 to harmonize echinocandin labeling. Cancidas labeling was otherwise last updated in August 2013 with changes not pertaining to safety.

[2] Cornely OA, Vehreschild JJ, Vehreschild MJ, Wurthwein G, Arenz D, Schwartz S, et al. Phase II dose escalation study of caspofungin for invasive Aspergillosis. Antimicrob Agents Chemother 2011 Dec;55(12):5798-803.

[3] Kohno S, Izumikawa K, Yoshida M, Takesue Y, Oka S, Kamei K, et al. A double-blind comparative study of the safety and efficacy of caspofungin versus micafungin in the treatment of candidiasis and aspergillosis. Eur J Clin Microbiol Infect Dis 2013 Mar;32(3):387-97.

Reference ID: 3631442

In conclusion, no new safety information was identified in the literature or in annual PSURs that would alter the favorable risk/benefit assessment of Cancidas/caspofungin.

L-arginine

The proposed new caspofungin formulation substitutes L-arginine for sucrose and mannitol in the RLD. The sponsor did not include specific safety information pertaining to this substitution.

Reviewer's Comments

L-arginine is an amino acid present in food, especially soy, milk, eggs, seafood and nuts. A 200 calorie serving of turkey or shrimp or 100 grams of peanuts for example contains approximately 3000 mg L-arginine[4]. It has been conservatively estimated that the average American diet contains 5400 mg of L-arginine per day[5]. The bioavailability of oral L-arginine following a 10 gm dose is 20%[6]. Assuming the same bioavailability, the systemic exposure resulting from the average American diet is approximately 1000 mg, 10 fold higher than the exposure resulting from 100 mg IV dose in this caspofungin preparation.

L-arginine is included as an excipient in at least one drug product, Veletri (esoprostenol, NDA 222260), approved in June 2008 for the treatment of pulmonary arterial hypertension. The approved dose is 2ng/kg/min increased by 2ng/kg/min until intolerance is noted. The mean dose at the conclusion of the 12-week clinical trials was approximately 10ng/kg/min (9.2 in one trial and 11.2 in another trial). Each 0.5 mg Veletri vial contains 50 mg arginine[7]. For a 70-kg person receiving a dose of 10ng/kg/min, the daily L-arginine exposure is 100 mg, similar to the daily exposure to L-arginine resulting from this caspofungin preparation.

Arginine is also marketed for injection under the brand name R-Gene 10 (NDA 016931). It is used as a diagnostic test to stimulate the pituitary gland to release growth hormone. The recommended dose is 30 grams for adults and 0.5 g/kg for children, administered over 30 minutes. AEs listed in the product package insert include allergic and hypersensitivity reaction, exacerbation of acrocyanosis and decreased platelet count, each occurring in one patient out of 1670[8]. The package insert does not report plasma concentrations of L-arginine resulting from the infusion.

L-arginine is marketed in several homeopathic products and in oral supplements to be taken at doses up to 30 grams daily, with health claims including reduction of blood pressure and cholesterol, prevention of heart attacks and strokes, and treatment of erectile dysfunction[9,10].

[4] http://nutritiondata.self.com/foods-00008900000000000000 html
[5] Visek, W. Arginine needs, physiologic state and usual diets. A reevaluation. J Nutrition 1986;116:36-46
[6] Tangphao O, Gorssman M, Chalon S, Hofman B, Blaschke T. Pharmacokinetics of intravenous and oral L-arginine in normal volunteers. Br J Clin Pharmacol 1999;47:261-266
[7] http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022260s005lbl.pdf
[8] http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/016931s031lbl.pdf
[9] http://www.naturalstandard.com/databases/herbssupplements/arginine.asp
[10] http://www.drugs.com/npc/l-arginine html

Reference ID: 3631442

The major portion of dietary L-arginine is utilized by the liver in the hepatic urea cycle and a small part is metabolized by nitric oxide synthase to L-citrulline and nitric oxide (NO). Because NO is a vasodilator, L-arginine has been investigated as potential therapy for patients with atherosclerotic disease. However, a review of the PK/PD properties of arginine indicates that oral doses below 15 grams do not have demonstrable physiologic effects[11]. The majority of the studies reported in the literature were done in patients in the post-myocardial infarction period or in patients with heart failure. In one study, 792 patients with CAD were given placebo or L-arginine 9 grams orally daily for one month 24 hours after an acute MI. There was no statistically significant difference in the composite endpoint of death, re-infarction, recurrent myocardial ischemia, successful resuscitation or pulmonary edema. Overall adverse events were not significantly different between the groups[12]. In another study, 153 patients 3-21 days post ST elevation myocardial infarction received 1 gm tid of L-arginine for one week, followed by 2 gm tid for one week, then 3 gm tid for the third week then for 6 months. Common AE were similar in the group that received arginine (78 patients) or placebo (75 patients) and there were no significant changes in vascular stiffness measurements or in left ventricular ejection fraction between the two groups. However, 6 participants in the arginine arm (7.8%) died compared to none in the placebo arm prompting the data safety committee to close the study. Five of the six deaths were in patients older than 60 years of age. Causes of death included myocardial rupture due to re-infarction (1), sepsis (2), sudden death 3 weeks after end of treatment (1) and unknown (2). The authors concluded that the drug should not be recommended following an acute MI[13].

IV infusion of 16 gm of L-arginine in patients with hypercholesterolemia did not affect indices of cardiovascular performance. No specific adverse reactions were reported[14]. Intravenous doses of 3, 6 and 12 gm of L-arginine were given in addition to quinine therapy to three separate cohorts of 10 adults with severe *Plasmodium falciparum* malaria[15]. No clinically significant hemodynamic or biochemical adverse reactions were observed.

In conclusion, the exposure to L-arginine resulting from this caspofungin preparation is lower than the exposure resulting from average dietary intake and similar to exposures from the administration of at least one approved product for the treatment of pulmonary artery hypertension. Considerably higher IV exposures have been reported in the literature in patients with hypercholesterolemia or malaria without specific adverse reactions. Oral doses lower than 15 grams do not seem to have significant hemodynamic effects, and assuming 20% bioavailability, the systemic exposure resulting from 15 grams given orally is equivalent to 3000 mg IV. L-arginine is available in oral supplements up to 30 grams daily, and with the exception of one report of possible increased mortality in post-MI patients who received 9

[11] Boger R. The pharmacodynamics of L-arginine. J Nutrition 2007;137:1650S-1655S
[12] Bednarz B, Jaxa-Chamied T, et al. Efficacy and safety of oral L-arginine in acute myocardial infarction. Results of the multicenter randomized, double-blind, placebo-controlled ARAMI pilot trial. Kardiol Pol. 2005;62:421-7
[13] Schulman S, Becker L, Kass D et al. L-arginine therapy in acute myocardial infacrtion. The vascular interaction with age in myocardial infarction (VINTAGE MI) randomized clinical trial. JAMA 2006;295:58-64
[14] Wennmalm A, Edlund A, Granstrom E, Wiklund O. Acute supplementation with the nitric oxide precursor L-arginine does not improve cardiovascular performance in patients with hypercholesterolemia. Atherosclerosis 1995;118:223-231
[15] Yeo T, Lampah D et al. Safety profile of L-arginine infusion in moderately severe falciparum malaria. PLoS One 2008;3:e2347

Reference ID: 3631442

grams daily for 6 months, no significant adverse reactions have been reported. The addition of L-arginine to this caspofungin preparation does not alter the favorable risk/benefit assessment of caspofungin in the treatment of the approved indications.

Labeling
Identical labeling to Cancidas is recommended for the Indications, Warnings, Adverse Events, and Clinical Studies sections.

Recommendations/Risk Benefit Assessment

The recommendation is to approve this preparation of caspofungin.

No new clinical or non-clinical studies were included in this submission. A waiver of bio-equivalency studies was granted; this formulation of caspofungin is assessed as bioequivalent to the approved RLD, Cancidas. 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.

No postmarketing Risk Evaluation and Management Strategies or postmarketing requirements or commitments are recommended.

Appendix 1

1. Ostrosky-Zeichner L, Shoham S, et al. MSG-01: A randomized, double-blind, placebo-controlled trial of caspofungin prophylaxis followed by preemptive therapy for invasive candidiasis in high risk adults in the critical care setting. Clin Infect Dis 2014;58:1219-1226

2. León-Gil C, Ubeda-Iglesias A, et al. ProCAS Study Group.Efficacy and safety of caspofungin in critically ill patients. ProCAS Study. Rev Esp Quimioter. 2012;25:274-82.

3. Kohno S, Izumikawa K, et al. A double-blind comparative study of the safety and efficacy of caspofungin versus micafungin in the treatment of candidiasis and aspergillosis. Eur J Clin Microbiol Infect Dis. 2013;32:387-97.

4. Döring M, Hartmann U, et al. Caspofungin as antifungal prophylaxis in pediatric patients undergoing allogeneic hematopoietic stem cell transplantation: a retrospective analysis. BMC Infect Dis. 2012;12:151.

5. Jarque I, Tormo M, et al. Spanish Pethema Group). Caspofungin for the treatment of invasive fungal disease in hematological patients (ProCAS Study) Med Mycol. 2013;51:150-4.

6. Caselli D, Cesaro S, et al. A prospective, randomized study of empirical antifungal therapy for the treatment of chemotherapy-induced febrile neutropenia in children. Br J Haematol. 2012;158:249-55.

7. Cornely OA, Vehreschild JJ, et al. Phase II dose escalation study of caspofungin for invasive Aspergillosis. Antimicrob Agents Chemother. 2011;55:5798-803

8. Cattaneo C, Monte S, et al. A randomized comparison of caspofungin versus antifungal prophylaxis according to investigator policy in acute leukaemia patients undergoing induction chemotherapy (PROFIL-C study). J Antimicrob Chemother. 2011;66:2140-5.

Reference ID: 3631442

9. Mohamed WA, Ismail M. A randomized, double-blind, prospective study of caspofungin vs. amphotericin B for the treatment of invasive candidiasis in newborn infants. J Trop Pediatr. 2012;58:25-30

10. Hiemenz JW, Raad II, et al. Efficacy of caspofungin as salvage therapy for invasive aspergillosis compared to standard therapy in a historical cohort. Eur J Clin Microbiol Infect Dis. 2010;29:1387-94

11. Migoya EM, Mistry GC, et al. Safety and pharmacokinetics of higher doses of caspofungin in healthy adult participants. J Clin Pharmacol. 2011;51:202-11

12. Groll AH, Silling G, et al. Randomized comparison of safety and pharmacokinetics of caspofungin, liposomal amphotericin B, and the combination of both in allogeneic hematopoietic stem cell recipients. Antimicrob Agents Chemother. 2010;54:4143-9

13. Maertens JA, Madero L, et al. Caspofungin Pediatric Study Group. A randomized, double-blind, multicenter study of caspofungin versus liposomal amphotericin B for empiric antifungal therapy in pediatric patients with persistent fever and neutropenia. Pediatr Infect Dis J. 2010;29:415-20

14. Winkler M, Pratschke J, et al. Caspofungin for post solid organ transplant invasive fungal disease: results of a retrospective observational study. Transpl Infect Dis. 2010;12:230-7

15. Herbrecht R, Maertens J, et al. Caspofungin first-line therapy for invasive aspergillosis in allogeneic hematopoietic stem cell transplant patients: an European Organisation for Research and Treatment of Cancer study. Bone Marrow Transplant. 2010;45:1227-33

16. Viscoli C, Herbrecht R, et al. Infectious Disease Group of the EORTC. An EORTC Phase II study of caspofungin as first-line therapy of invasive aspergillosis in haematological patients. J Antimicrob Chemother. 2009;64:1274-81

17. Betts RF, Nucci M, et al. Caspofungin High-Dose Study Group.A Multicenter, double-blind trial of a high-dose caspofungin treatment regimen versus a standard caspofungin treatment regimen for adult patients with invasive candidiasis. Clin Infect Dis. 2009;48:1676-84

18. Fortún J, Martín-Dávila P, et al. GESITRA Study Group. Prophylaxis with caspofungin for invasive fungal infections in high-risk liver transplant recipients. Transplantation. 2009;87:424-35

Reference ID: 3631442

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

/s/

HALA H SHAMSUDDIN
09/22/2014

THOMAS D SMITH
10/02/2014
I concur.