CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206110Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	206110/SDN 0019
Submission Date	October 31, 2016
Drug	Caspofungin Acetate for Injection
OCP Reviewer	Dakshina M. Chilukuri, PhD
OCP Team Leader	Seong H. Jang, PhD
OCP Division	DCP4
OND Division	DAIP
Applicant	Fresenius Kabi USA, LLC
Submission Type	505(b)(2)
Formulation	IV Formulation
Indication(s)	Treatment of fungal infections

1. EXECUTIVE SUMMARY

Caspofungin is a semisynthetic lipopeptide (echinocandin) compound synthesized from a fermentation product of *Glarea Lozoyensis*. Caspofungin inhibits the synthesis of beta (1,3)-D-glucan, an essential component of the cell wall of susceptible *Aspergillus* species and *Candida* species. Beta (1,3)-D-glucan is not present in mammalian cells. Caspofungin has shown activity against *Candida* species and in regions of active cell growth of the hyphae of *Aspergillus fumigatus*.

Caspofungin is marketed in the US as Cancidas® (NDA 021227, Merck & Co., Inc.) and approved for use in the treatment of candidemia and *Candida* infections including intra-abdominal abscesses, peritonitis, and pleural space infections; treatment of esophageal and oropharyngeal candidiasis; treatment of invasive aspergillosis in patients who are refractory or intolerant of other therapies; empirical therapy for presumed fungal infections in febrile, neutropenic patients. Caspofungin has been shown to be active both in vitro and in clinical infections against most strains of the following microorganisms: *Aspergillus fumigatus, Aspergillus flavus*, *Aspergillus terreus*, *Candida albicans*, *Candida glabrata*, *Candida guilliermondii*, *Candida krusei*, *Candida parapsilosis*, and *Candida tropicalis*

On December 27, 2013, the Applicant submitted a 505(b)(2) application NDA 206110 seeking approval of caspofungin acetate for the same indications as CANCIDAS®. This product was submitted to 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 76.6 mg in CANCIDAS®. This new formulation differs from CANCIDAS® in that the 50 mg vial contains 100 mg arginine and the 70 mg vial contains 140 mg arginine whereas CANCIDAS® contains sucrose and mannitol. No new studies were submitted in this application.

At the conclusion of the review cycle, the OPQ review team did not recommend approval because the information submitted to assure identity, strength, purity and quality of the drug

product were not sufficient. 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. 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 company (Merck) 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.

Overall Recommendations:

No new clinical pharmacology information was submitted in this 505(b)(2) NDA and there are no changes to the label pertinent to the clinical pharmacology sections. The clinical pharmacology team recommends approval of this 505(b)(2) NDA.

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/s/

DAKSHINA M CHILUKURI
12/12/2016

SEONG H JANG
12/12/2016

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 206-110	**Reviewer:** Houda Mahayni, Ph.D.	
Division:	DAIP		
Applicant:	Fresenius Kabi USA, LLC.	**Acting Team Leader:** Okpo Eradiri, Ph.D.	
Trade Name:	---	**Acting Supervisor:** Paul Seo, Ph.D.	
Generic Name:	Caspofungin Acetate for Injection, Lyophilized Powder, 50 mg/vial and 70 mg/vial	**Date Assigned:**	January 5, 2014
Indication:	Emperical therapy for presumed fungal infections in febrile, neutropenic patients; treatment of candidemia and Candida infections; treatment of esophageal candidiasis; and treatment of invasive aspergillosis	**Date of Review:**	September 15, 2014
Formulation/strength	Injection, 50 mg/vial and 70 mg/vial		
Route of Administration	Intravenous		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Dates:	GRMP Date	PDUFA Date
December 27, 2013 April 1, 2014 June 24, 2014 September 12, 2014	September 21, 2014	October 27, 2014
Type of Submission	505 (b) (2)	
Key review point	Evaluation of the Biowaiver request	

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I) SUMMARY OF BIOPHARMACEUTICS FINDINGS

Submission:

The Applicant (FK USA) submitted this original New Drug Application for Caspofungin Acetate injection under Section 505 (b) (2) of the Federal Food, Drug, and Cosmetic Act. The Applicant stated that the caspofungin concentration, route of administration, dose, and dosing regimen for the proposed product are identical to those of the RLD (Cancidas® (caspofungin acetate) (NDA 21227, Merck & Co., Inc.)).

The proposed formulation of caspofungin is a sterile lyophilized powder for reconstitution. The Applicant intends to commercialize two dosage strengths, 50 mg and 70 mg vials to be administered intravenously over a period of 60 minutes. The difference in the proposed product formulation as compared to the RLD (cancidas) is that L-arginine is used in place of the sucrose and mannitol found in Cancidas®. These excipients function as (b) (4) in the formulation.

Biowaiver:

The Applicant requested a waiver of *in vivo* bioavailability/bioequivalence (BA/BE) requirements for Caspofungin Acetate for Injection based on 21 CFR § 320.22 (b).

The Applicant provided scientific justification to demonstrate that using L-arginine in the proposed product in place of sucrose and mannitol found in Cancidas® is not expected to alter the pharmacokinetics or pharmacodynamics of caspofungin.

This Biopharmaceutics review evaluated the acceptability of the biowaiver request and found the Applicant's justification acceptable to grant the biowaiver.

Risk Evalutation:

Risk Assessment Table

From Biopharmaceutics Assessment			***Review Assessment***		
Product attribute/ CQA	***Factors that can impact the CQA***	***Risk Ranking***	***Risk Mitigation approach***	***Risk Evaluation***	***Lifecycle Considerations/ Comments***
Osmolality	***None identified***	***L***	***None***	***Acceptable***	***Similar osmolality values were obtained comparing the osmolality of the RLD and the proposed product***

pH	***None identified***	***L***	***None***	***Acceptable***	***Similar pH values were obtained comparing the pH of the RLD, and the proposed product pH test and limits are included in the finished product specification table***

II) RECOMMENDATION

The ONDQA-Biopharmaceutics team has reviewed NDA 206-110 for Caspofungin Acetate for Injection, 50 mg and 70 mg and find the biowaiver request acceptable. Therefore, the biowaiver is granted.

From the Biopharmaceutics perspective, NDA 206-110 is recommended for APPROVAL.

Houda Mahayni, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Okpo Eradiri, Ph.D.
Acting Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: DARRTS/Seo

III) BIOPHARMACEUTICS ASSESSMENT-QUESTION BASED REVIEW APPROACH

A) GENERAL ATTRIBUTES

a. What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility)?

Caspofungin acetate is freely soluble in water and methanol, but slightly soluble in ethanol. The Applicant stated that caspofungin is amorphous and hygroscopic. (b) (4)

b. What is the route of administration? How is the product being administered?

The proposed formulation of caspofungin is a sterile lyophilized powder for reconstitution. The product must be reconstituted with 10.8 mL of 0.9% Sodium Chloride Injection, Sterile Water for Injection, Bacteriostatic Water for Injection with methylparaben and propylparaben, or Bacteriostatic Water for Injection with 0.9% benzyl alcohol before further diluted to NMT 0.5 mg/mL in 0.9%, 0.45%, or 0.225% Sodium Chloride Injection or Lactated Ringers Injection. The reconstituted solution is intended to be infused intravenously over 60 minutes. An initial loading dose of 70 mg is administered on day 1 of treatment followed by administration of 50 mg daily until resolution of the infection.

c. Does the drug product include a delivery device?

No.

B) DRUG PRODUCT FORMULATION

d. What is the formulation?

The Applicant intends to commercialize two dosage strengths, 50 mg and 70 mg vials. Table 1 and Table 2 list the component and compositions of the 50 mg/vial and 70 mg/vial, respectively.

Also, the Applicant stated that the commercial scale-up process contains the same unit operations and utilizes equipment of the same design and operating principles as used to produce the exhibit batches.

Table 1: Components and composition of the 50 mg/vial dosage strength

Strength	50 mg/vial		
Packaging Configuration	Lyophilized powder or cake in a 10 cc vial		
Vial	10 cc (b) (4), glass (b) (4) Type 1, 20 mm (b) (4)		
Stopper	20 mm, (b) (4) rubber		
Seal	20 mm, Flip-off Aluminum crimp seal		
Drug Product Name	**Content (per vial)**	**Function**	**Quality of Ingredient**
Caspofungin Acetate	50 mg	Active Pharmaceutical Ingredient	Non-compendial
L-Arginine, USP	100 mg	(b) (4)	USP
(b) (4)			NF
			USP
Hydrochloric Acid, NF	As required	pH adjuster	NF
Sodium Hydroxide, NF	As required	pH adjuster	NF

(b) (4)

Table 2: Components and composition of the 70 mg/vial dosage strength

Strength	70 mg/vial		
Packaging Configuration	Lyophilized cake or powder in a 10 cc vial		
Vial	10 cc (b) (4), glass (b) (4) Type 1, 20 mm (b) (4)		
Stopper	20 mm, (b) (4) rubber		
Seal	20 mm, Flip-off Aluminum crimp seal		
Drug Product Name	**Content (per vial)**	**Function**	**Quality of Ingredient**
Caspofungin Acetate	70 mg	Active Pharmaceutical Ingredient	Non-compendial
L-Arginine, USP	140 mg	(b) (4)	USP
(b) (4)			NF
			USP
Hydrochloric Acid, NF	As required	pH adjuster	NF
Sodium Hydroxide, NF	As required	pH adjuster	NF

(b) (4)

e. What are the highlights of the drug product formulation development?

The difference in the proposed product formulation as compared to the RLD (Cancidas®) is that L-arginine is used in place of the sucrose and mannitol found in Cancidas®. Table 3 compares the RLD and proposed formulations.

Table 3: Formulation comparison between the RLD and proposed formulations

Ingredients	Cancidas® (mg/vial)		FK USA (mg/vial)		Function of Ingredients
	50 mg/vial	70 mg/vial	50 mg/vial	70 mg/vial	
Caspofungin Acetate	50	70	50	70	Therapeutic agent
Sucrose	39	54	N/A	N/A	(b) (4)
Mannitol	26	36	N/A	N/A	
Arginine	N/A	N/A	100 mg	140 mg	
Glacial Acetic Acid	As needed	As needed	N/A	N/A	
Sodium Hydroxide	N/A	N/A	As needed	As needed	pH adjuster
Hydrochloric Acid	N/A	N/A	As needed	As needed	pH adjuster
(b) (4)					

C) SUPPORTIVE INFORMATION

f. What data are available to support the approval of the proposed product?

This new drug application (NDA) for the proposed lyophilized caspofungin product is submitted under the 505(b) (2) regulatory pathway. The Applicant intends to rely upon FDA's findings of safety and efficacy for the listed drug, Cancidas®, and the information in the Cancidas® labeling to support the approval of this application. The caspofungin concentration, route of administration, dose, and dosing regimen of the proposed product are identical to those of the RLD Cancidas® (NDA 021227).

The proposed product is intended to be administered as a solution of the same dosage strength and at the same dose as that of the RLD. The difference in the proposed product formulation as compared to the RLD (Cancidas®) is in the (b) (4) The Applicant substituted in the proposed product formulation the (b) (4), L-arginine, for the (b) (4)s, sucrose and mannitol. According to the Applicant, this substitution is not expected to affect the excretion, metabolism, and/or distribution and therefore will not affect the systemic exposure or the pharmacologic activity of caspofungin. The Applicant stated that the 2 formulations (proposed and RLD) are considered to be therapeutic equivalents.

The following is a summary of the Applicant's 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 (sources: \\cdsesub1\evsprod\nda206110\0000\m2\27-clin-sum\summary-biopharm-pdf.pdf; and \\cdsesub1\evsprod\nda206110\0000\m1\us\112-other-corr\request-for-waiver.pdf):

- Each 50 mg vial contains (b) (4) mg L-arginine and each 70 contains (b) (4) mg L-arginine after reconstitution. Therefore, a loading dose in adults contains (b) (4) mg L-arginine and maintenance doses contain (b) (4) mg L-arginine.
- The daily uptake of L-arginine through the diet is about 4 – 6 g/day, and L-arginine oral bioavailability ranges from 50% – 80%. Therefore, it can be assumed that a significant amount of this orally consumed L-arginine would enter the systemic circulation.
- Based on the dosing regimen of caspofungin, the maximum of (b) (4) mg L-arginine in a single day is significantly less than the dose consumed on a typical day from the diet.
- L-arginine is the active ingredient in the approved drug product R-GENE® 10, NDA 016931, Pharmacia and Upjohn. The dosage regimen of R-GENE® is 30 g/day which is (b) (4) higher than the (b) (4) mg/day maximum daily dose of L-arginine in the proposed product.

- L-arginine is a precursor of NO synthesis which can change blood pressure by inducing vasodilation through stimulation of NO production. This pharmacodynamics effect of L-arginine has the potential to affect hepatic perfusion and renal clearance through modulation of blood flow through those organs. Caspofungin is eliminated through biliary and renal excretion, with approximately 35% of radiolabeled caspofungin measured in the feces and 41% in urine following a single IV dose. Therefore, it is possible that alterations in hepatic or renal perfusion can effect elimination of capsofungin. However, the dose reported in the literature to affect blood pressure is 6-30 g/day IV, while the maximum dose of L-arginine from the proposed product is (b) (4) mg/day. The L-arginine dose from the proposed product is approximately (b) (4) lower than the lowest pharmacodynamically relevant L-arginine dose.
- The Applicant stated that accumulation of L-arginine is not expected due to the relatively rapid elimination of intravenous L-arginine with elimination half-life of 40-60 minutes.
- The pharmacologically active dose ((b) g IV), and the dose of L-arginine from the proposed product ((b) (4) mg) which is too low to significantly alter hemodynamics or elimination of caspofungin.
- The Applicant stated that the proposed product is considered safe because L-arginine at (b) (4)% has been used in an FDA approved IV injection product. Whereas, L-Arginine in the 50 mg and 70 mg in the proposed drug product are at a level of (b) (4)% which is less than other approved IV injection product. Also, the maximum daily dose of L-arginine administered for an FDA-approved drug product, Aztreonam for Injection, is 6.2 g. Whereas, the daily dose of L-arginine in the proposed product for the maintenance dose of 50 mg (b) (4) mg L-arginine) and the loading dose of 70 mg (b) (4) mg L-arginine).

The Applicant concludes that the intake of L-arginine from the proposed product is comparable to the clinical dose from an approved intravenous drug product and typical daily intake from food. Therefore, substitution of L-arginine for sucrose and mannitol would not be expected to affect the systemic exposure or the pharmacologic activity of caspofungin. Also, the daily doses of L-arginine in the proposed product are considered to be safe.

Reviewer's Comment:

This reviewer confirmed with the clinical reviewer, Dr. Hala Shamsuddin, that the level of L-arginine in the drug product (50 mg and 70 mg) are considered to be safe. Also, this reviewer confirmed with the clinical pharmacology reviewer, Dr. Dakshina M. Chilukuri, that L-arginine is not expected to affect the systemic exposure or the pharmacologic activity of caspofungin (see Dr. Dakshina M. Chilukuri's review in DARRTS dated 9/12/2014). Therefore, the scientific justification provided above support the approval of the proposed product.

g. Does the Applicant rely on the safety and/or efficacy of a reference product?

Yes, the Applicant relies upon FDA's findings of safety and efficacy for the RLD, Cancidas®, to support the approval of this application.

h. Was a bioequivalence study conducted? If yes, is a Biopharmaceutics Review needed for the submission?

No, the Applicant did not conduct any in vivo studies to support their product. However, the Applicant provided analytical and literature data to support that the pharmacokinetic and pharmacodynamics profiles of the propose product should not differ significantly from the RLD.

D) BIOWAIVER

i. Is there a waiver request for the submission of in vivo BA/BE data (biowaiver)?

Yes, the Applicant is requesting a biowaiver from the requirements for submission of *in vivo* bioavailability or bioequivalence data. The justification for the biowaiver request is provided under (*f*) above.

j. What is the purpose of the biowaiver request?

Pursuant to 21 CFR § 320.22(b) (1), the Applicant requests a waiver from the requirements for submission of *in vivo* bioavailability or bioequivalence data. The drug product is a solution intended to be administered via the same route, at the same dose, and for the same indications as the RLD Cancidas®. The proposed product is identical to the RLD except for the substitution of L-arginine in the proposed product for sucrose and mannitol in the RLD (Cancidas®). This substitution of the (b) (4) in the proposed product is expected to produce equivalent relative systemic exposure to that of the RLD.

k. What information supports the biowaiver request?

The Applicant provided the information to support the biowaiver request listed under (*f*) above. Therefore, FDA requested the following information in the Filing Communicated dated March 11, 2014:

1. *We are concerned about the differences in the inactive ingredients between the proposed product and the RLD, specifically the effect that the lack of mannitol may have on the disposition of your proposed product in relation to the listed drug product. To address our concerns, please provide information/justification supporting that the in vivo physiological disposition (metabolism and excretion) of caspofungin from your proposed product formulated without*

mannitol will not be different than that of the listed drug product. You may include published literature references to support your justification.

2. *Provide adequate comparative physicochemical property data such as comparison of osmolality and pH of the proposed drug product and the listed drug product (side-by side table). The comparative data for the proposed drug product and listed drug product should be provided using at least 3 production lots (if available) of the proposed drug product and 3 commercial lots of the listed drug product. The measurements should be done in triplicate for each lot tested.*

On April 1, 2014, the Applicant submitted a request for an extension to respond to FDA's request until June 2014, and provided the following information (in Italic):

Comparative Data for the pH

During the reconstituted solution stability study, the pH of the reconstituted solutions for both the proposed and RLD product samples were not significantly different, as shown in Table 1.

TABLE I: pH of Reconstituted Caspofungin Acetate for Injection

Diluent Used for Reconstitution		pH Range Found during Reconstituted Solution[2] Stability Testing (Proposed Limit: (b) (4) in SWFI)		
Diluent Name[1]	USP pH Spec for the diluent	FK USA 50 mg/vial	FK USA 70 mg/vial	RLD 70 mg/vial
NS	4.5 – 7.0	(b) (4)		
SWFI	(b) (4)			
BWFI-MP				
BWFI-BA				

1 NS = 0.9% Sodium Chloride Injection, USP; SWFI = Sterile Water for Injection, USP; BWFI-MP = Bacteriostatic Water for Injection, USP, containing Methylparaben and Propylparaben; BWFI-BA = Bacteriostatic Water for Injection, USP, containing Benzyl Alcohol.

2 Detailed study can be found in PR-13-00394 Final Report submitted in the original NDA.

The above result can be found in the following report:
\\cdsesub1\evsprod\nda206110\0000\m3\32-body-data\32p-drug-prod\caspofunginacetateforinj-sterilelyo50mg\32p2-pharm-dev\pharmaceutical-development-lvp-pr-13-00394.pdf.

Also, during the LVP admixture compatibility study, the pH between the reconstituted solutions and the corresponding LVP admixtures was not significantly different, as shown in Table II below.

TABLE II: pH of FK USA Caspofungin Acetate for Injection LVP Mixtures[2]

Reconstitution Diluent[1]	pH of FK Product Reconstituted Solution	LVP Diluent[1]	USP pH Spec for the LVP Diluent	pH of FK USA Product LVP Admixture
BWFI-MP	(b) (4)	NS	4.5 – 7.0	(b) (4)
BWFI-BA				
BWFI-MP		LRI	(b) (4)	
BWFI-BA				

1 NS = 0.9% Sodium Chloride Injection, USP; SWFI = Sterile Water for Injection, USP; BWFI-MP = Bacteriostatic Water for Injection, USP, containing Methylparaben and Propylparaben; BWFI-BA = Bacteriostatic Water for Injection, USP, containing Benzyl Alcohol; LRI = Lactated Ringer's Injection, USP.

2 Detailed study can be found in PR-13-00394 Final Report submitted in the original NDA.

Because the study showed no significant difference in pH results of the reconstituted solutions between proposed and RLD products (TABLE I) and no significant difference between pH results of the reconstituted solutions and the corresponding LVP admixtures (TABLE II) of the proposed product, it is not expected to see significant difference in pH results of LVP admixtures between the proposed and RLD products. However, in response to FDA request, additional LVP admixture testing for pH comparing the proposed product with RLD will be performed in one selected reconstitution diluent (0.9% Sodium Chloride Injection) in combination with 2 LVP diluents (0.9% Sodium Chloride Injection having USP pH Limit of 4.5 – 7.0 and Lactated Ringer's Injection having USP pH Limit of 6.0 – 7.5), using 3 different lots of RLD and 3 exhibit batches of the proposed product. Each lot will be tested for individual product vials.

Comparative Data for the Osmolarity

Based on theoretical calculation (TABLE III) of osmolarity contributions from different excipients used in the proposed product and RLD, it is predicted that the difference in osmolarity of the LVP admixtures of the two products (proposed and RLD) is negligible. However, in response to FDA request, a study will be performed on LVP admixture to compare the osmolality of the proposed product to the RLD in one selected reconstitution diluent (0.9% Sodium Chloride Injection having highest osmolarity) in combination with 2 LVP diluents (0.9% Sodium Chloride Injection having osmolarity of 308 mOsmo/L and Lactated Ringer's Injection having osmolarity of 273 mOsmo/L), using 3 different lots of RLD and 3 exhibit batches of the proposed product. Each lot will be tested for 3 individual product vials.

TABLE III: Calculated Osmolarity Contribution from Different Excipients Used in FK USA and RLD Products

Concentrations of Excipients in LVP admixture			Osmolarity contributed from the excipient(s) (mOsmo/L)[1]	
Excipients	mg/mL	(mmol)	FK USA Product	RLD Product
Mannitol (M.W. = (b) (4)		(b) (4)	N/A	(b) (4)
Sucrose (M.W. =			N/A	
Arginine (M.W. =			(b) (4)	N/A
Subtotal		N/A		(b) (4)

(b) (4)

On June 24, 2014, the Applicant provided the complete responses to items 1 and 2 under (*k*) above which were requested in the Filing Communication dated March 11, 2014.

The summary response to item 1 is as follows: (source: \\cdsesub1\evsprod\nda206110\0005\m1\us\111-info-amend\quality-info-amend.pdf)

(b) (4)

The summary response to item 2 is as follows: (source: \\cdsesub1\evsprod\nda206110\0005\m1\us\111-info-amend\quality-info-amend.pdf)

Comparative Data for the pH

- The Applicant performed LVP admixture testing for pH comparing the proposed product with RLD in one selected reconstitution diluent (0.9% Sodium Chloride Injection) in combination with 2 LVP diluents (0.9% Sodium Chloride Injection having USP pH Limit of 4.5 – 7.0 and Lactated Ringer's Injection having USP pH Limit of 6.0 – 7.5), using 3 different lots of RLD and 3 exhibit batches of the proposed product. Each lot has been tested for 3 individual product vials.
- pH test results are provided in TABLE 1.11.1- 3 and TABLE 1.11.1- 4. The Applicant concluded that all pH testing results from LVP admixtures prepared using RLD and the proposed product met the USP pH limits for the LVP diluents, which are 4.5 to 7.0 and 6.0 to 7.5 for 0.9% Sodium Chloride Injection and Lactated Ringer's Injection, respectively.

Table 1.11.1- 3 Comparison of pH of Drug Product LVP Admixtures in 0.9% Sodium Chloride Injection (pH Limit: (b) (4) (Source: quality-info-amend.pdf)

Product Name	Lot Number	Diluent for Reconstitution	LVP Diluent	Test Date	pH Results of LVP Mixture
Caspofungin Acetate for Injection (exhibit lots)	R342-035	0.9% Sodium Chloride Injection	0.9% Sodium Chloride Injection	(b) (4)	(b) (4)
	R342-042				
	R342-043				
Cancidas® (RLD)	215590 (Exp.06/2015)				
	2112610 (Exp. 09/2015)				
	2130980 (Exp. 10/2015)				

Table 1.11.1- 4 Comparison of pH of Drug Product LVP Admixtures in Lactated Ringer's Injection (pH Limit: 6.0 to 7.5) (Source: quality-info-amend.pdf)

Product Name	Lot Number	Diluent for Reconstitution	LVP Diluent	Test Date	pH Results of LVP Mixture
Caspofungin Acetate for Injection (exhibit lots)	R342-035	0.9% Sodium Chloride Injection	0.9% Sodium Chloride Injection	[redacted] (b) (4)	
	R342-042				
	R342-043				
Cancidas® (RLD)	215590 (Exp.06/2015)				
	2112610 (Exp. 09/2015)				
	2130980 (Exp. 10/2015)				

Comparative Data for the Osmolarity

- The Applicant performed LVP admixture testing for osmolarity comparing the proposed product with RLD in one selected reconstitution diluent (0.9% Sodium Chloride Injection having highest osmolarity) in combination with 2 LVP diluents (0.9% Sodium Chloride Injection having osmolarity of 308 mOsmo/L and Lactated Ringer's Injection having osmolarity of 273 mOsmo/L), using 3 different lots of RLD and 3 exhibit batches of the proposed product. Each lot has been tested for 3 individual product vials.
- The Applicant concluded that all osmolarity results from LVP admixtures prepared in 0.9% Sodium Chloride Injection using RLD and the proposed product (TABLE 1.11.1-6) are close to the Osmolarity of 308 mOsmol/L for 0.9% Sodium Chloride Injection and are well within the Osmolality range of normal physiological system. Also, the osmolarity results from LVP admixtures prepared in Lactated Ringer's Injection using RLD and the proposed product (TABLE 1.11.1- 7) are similar to the osmolality of 273

mOsmol/L for Lactated Ringer's Injection and slightly below the Osmolality of normal physiological system.

Table 1.11.1- 6 Comparison of Osmolality of Drug Product LVP Admixtures in 0.9% Sodium Chloride Injection (Osmolarity of Normal Physiological Range: (b) (4) mOsmol/L) (Source: quality-info-amend.pdf)

Product Name	Lot Number	Diluent for Reconstitution	LVP Diluent	Test Date	Osmolality Results of LVP Admixture (mOsmol/kg)[1]
Caspofungin Acetate for Injection (exhibit lots)	R342-035	0.9% Sodium Chloride Injection	0.9% Sodium Chloride Injection	(b) (4)	
	R342-042				
	R342-043				
Cancidas® (RLD)	215590 (Exp.06/2015)				
	2112610 (Exp. 09/2015)				
	2130980 (Exp. 10/2015)				

[1] Test results are measured as Osmolality (mOsmol per kilogram of solution)

Table 1.11.1- 7 Comparison of Osmolality of Drug Product LVP Admixtures in Lactated Ringer's Injection (Osmolarity of Normal Physiological Range: (b) (4) mOsmol/L) (Source: quality-info-amend.pdf)

Product Name	Lot Number	Diluent for Reconstitution	LVP Diluent	Test Date	Osmolality Results of LVP Admixture (mOsmol/kg)[1]
Caspofungin Acetate for Injection (exhibit lots)	R342-035	0.9% Sodium Chloride Injection	0.9% Sodium Chloride Injection	(b) (4)	
	R342-042				
	R342-043				
Cancidas® (RLD)	215590 (Exp.06/2015)				
	2112610 (Exp. 09/2015)				
	2130980 (Exp. 10/2015)				

[1] Test results are measured as Osmolality (mOsmol per kilogram of solution)

The Applicant concluded that the physicochemical property data such as pH and osmolarity of the proposed drug product is comparable to RLD product.

<u>Reviewer's Overall Assessment</u>: SATISFACTORY.

The comparative pH data show that Cancidas® has a slightly lower pH than the proposed product. However, this difference is considered insignificant given the variation of pH units between Cancidas® and the proposed product are between (b) (4) in 0.9% Sodium Chloride Injection; and between (b) (4) in Lactated Ringer's Injection. These differences in pH units are considered acceptable.

The comparative osmolarity data also show similar trend as the Cancidas® has slightly lower osmolarity values than the proposed product. However, this difference is also considered insignificant given that variation of osmolarity

between Cancidas® and the proposed product are (b) (4) Osmol/kg in 0.9% Sodium Chloride Injection; and between (b) (4) mOsmol/kg in Lactated Ringer's Injection. These differences in osmolarity are considered acceptable and within the acceptable osmolarity range of normal physiological system.

It is noted that Table 1.11.1- 4 and Table 1.11.1- 7 above listed 0.9% Sodium Chloride as the LVP diluent instead of Lactated Ringer's Injection in both tables. On September 11, 2014, this observation was communicated to the Applicant. On September 12, 2014, the Applicant made the correction, as provided below

Table 1.11.1-4 Comparison of pH of Drug Product LVP Admixtures in Lactated Ringer's Injection (pH Limit: (b) (4)

Product Name	Lot Number	Diluent for Reconstitution	LVP Diluent	Test Date	pH Results of LVP Mixture
Caspofungin Acetate for Injection (exhibit lots)	R342-035	0.9% Sodium Chloride Injection	*Lactated Ringer's Injection*	(b) (4)	
	R342-042				
	R342-043				
Cancidas® (RLD)	215590 (Exp.06/2015)				
	2112610 (Exp. 09/2015)				
	2130980 (Exp. 10/2015)				

Table 1.11.1-7 Comparison of Osmolality of Drug Product LVP Admixtures in 0.9% Sodium Chloride Injection (Osmolarity of Normal Physiological Range: 280 to 310 mOsmol/L)

Product Name	Lot Number	Diluent for Reconstitution	LVP Diluent	Test Date	Osmolality Results of LVP Admixture (mOsmol/kg)[1]
Caspofungin Acetate for Injection (exhibit lots)	R342-035	0.9% Sodium Chloride Injection	*Lactated Ringer's Injection*	(b) (4)	
	R342-042				
	R342-043				
Cancidas® (RLD)	215590 (Exp.06/2015)				
	2112610 (Exp. 09/2015)				
	2130980 (Exp. 10/2015)				

[1] Test results are measured as Osmolality (mOsmol per kilogram of solution)

l. Are the CFR requirements for granting a biowaiver met? If not, are the provided justification and supportive data appropriate?

Yes.

m. Is the overall information supporting the biowaiver request acceptable?

Yes.

n. Is the biowaiver granted?

Yes.

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/s/

HOUDA MAHAYNI
09/16/2014

OKPONANABOFA ERADIRI
09/17/2014

CLINICAL PHARMACOLOGY REVIEW

NDA	206110
Submission Date	December 12, 2013
Drug	Caspofungin Acetate for Injection
OCP Reviewer	Dakshina M. Chilukuri, PhD
OCP Team Leader	Philip M. Colangelo, PharmD, PhD
OCP Division	DCP4
OND Division	DAIP
Applicant	Fresenius Kabi USA, LLC
Submission Type	505(b)(2)
Formulation	IV Formulation
Indication(s)	Treatment of fungal infections

1. EXECUTIVE SUMMARY

Caspofungin is a semisynthetic lipopeptide (echinocandin) compound synthesized from a fermentation product of *Glarea Lozoyensis*. Caspofungin inhibits the synthesis of beta (1,3)-D-glucan, an essential component of the cell wall of susceptible *Aspergillus* species and *Candida* species. Beta (1,3)-D-glucan is not present in mammalian cells. Caspofungin has shown activity against *Candida* species and in regions of active cell growth of the hyphae of *Aspergillus fumigatus*.

Caspofungin is marketed in the US as Cancidas® (NDA 021227, Merck & Co., Inc.) and is approved for use in the treatment of candidemia and *Candida* infections including intra-abdominal abscesses, peritonitis, and pleural space infections; treatment of esophageal and oropharyngeal candidiasis; treatment of invasive aspergillosis in patients who are refractory or intolerant of other therapies; empirical therapy for presumed fungal infections in febrile, neutropenic patients. Caspofungin has been shown to be active both in vitro and in clinical infections against most strains of the following microorganisms: *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus terreus*, *Candida albicans*, *Candida glabrata*, *Candida guilliermondii*, *Candida krusei*, *Candida parapsilosis*, and *Candida tropicalis*

Fresenius Kabi USA, LLC submitted a 505(b)(2) application on December 12, 2013. The reference listed drug product (RLD) is Cancidas (caspofungin acetate for injection 50 mg/vial and 70 mg/vial, a sterile lyophilized powder, injectable). The applicant's product contains caspofungin and is intended to be administered intravenously over a period of 60 minutes at the same dosage regimen as Cancidas. An initial loading dose of 70 mg is administered on day 1 of treatment followed by administration of 50 mg daily until resolution of the infection. The applicant's proposed formulation substitutes L-arginine for the sucrose and mannitol found in Cancidas.

Given that the proposed caspofungin product is to be administered as a solution via intravenous infusion, there should be no difference in the systemic exposure, safety, or

efficacy of the applicant's product compared with Cancidas. The applicant's product is intended to be administered as a solution of the same dosage strength and at the same dose as that of Cancidas. The only difference in the formulation compared with the Cancidas is the substitution of L-arginine for sucrose and mannitol as a (b) (4). This substitution is not expected to affect the excretion, metabolism, and/or distribution and therefore will not affect the systemic exposure (both C_{max} and AUC) to caspofungin or the pharmacologic activity of caspofungin. The 2 formulations are expected to be therapeutic equivalents.

Because the proposed formulation is expected to be therapeutically equivalent to Cancidas, the applicant has not conducted any in vivo studies to support their product. Instead, the applicant is relying upon the information presented in the Cancidas approved labeling and on the Agency's finding of safety and efficacy for Cancidas, to support its proposed caspofungin product. Further supportive information was provided from published literature available in the public domain, which includes several prospective and retrospective analyses of clinical safety and efficacy, clinical and nonclinical pharmacokinetic studies, and nonclinical pharmacology and toxicology studies with caspofungin.

The applicant did not submit any new clinical pharmacology information with this NDA. A request for a biowaiver was submitted and this was reviewed by ONDQA-Biopharm reviewer. The label submitted by the applicant contained no new changes to the clinical pharmacology section.

2. RECOMMENDATIONS

No new clinical pharmacology was submitted by the applicant in this NDA and thus, the clinical pharmacology team has no additional comments on this submission, and recommends approval of this 505(b)(2) NDA.

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/s/

DAKSHINA M CHILUKURI
09/11/2014

PHILIP M COLANGELO
09/12/2014