DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-227/S-023

Merck Research Laboratories
Attention: Chitrananda Abeygunawardana, Ph.D.
Associate Director, Regulatory Affairs
PO Box 1000
UG2D-068
North Wales PA 19454

Dear Dr. Abeygunawardana:

Please refer to your supplemental new drug application (sNDA) dated and received September 4, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CANCIDAS™ (caspofungin acetate) for Injection, 50mg/vial and 70 mg/vial.

We acknowledge receipt of your submissions dated:

October 27, 2008	November 4, 2008	February 12, 2009
October 28, 2008	November 10, 2008	May 19, 2009
October 30, 2008	November 26, 2008	June 11, 2009
November 3, 2008	January 26, 2009	June 23, 2009

This supplemental new drug application provides for the inclusion of information in the package insert on the 150 mg dose of CANCIDAS in patients with candidemia and invasive *Candida* infections. In addition, a number of editorial updates and revisions to the PLR (physician's labeling rule) format and content have been made, and these include revisions to the **HIGHLIGHTS OF PRESCRIBING INFORMATION**, **FULL PRESCRIBING INFORMATION:CONTENTS** and **FULL PRESCRIBING INFORMATION** sections of the package insert as follows (Additions are noted by underline and deletions are noted by ~~strikethrough~~):

(1) HIGHLIGHTS OF PRESCRIBING INFORMATION:

The name is revised as follows:

CANCIDAS (caspofungin acetate) for Injection (~~IV Infusion Only)~~ for intravenous use

The **RECENT MAJOR CHANGES** section is revised as follows:

Indications and Usage (1)	7/2008
Dosage and Administration,	
Recommended dosing in Adult Patients (2.2)	7/2009
Recommended Dosing in Pediatric Patients (>3 months of age) (2.3)	7/2008
Preparation and Reconstitution of CANCIDAS for Infusion (2.6)	7/2008

~~Special Considerations for Pediatric Patients >3 Months of Age (2.6)~~

The **DOSAGE AND ADMINISTRATION** section is revised as follows:

For All Patients (2.1):

- Administer by slow intravenous (IV) infusion ~~(IV)~~ over approximately 1 hour. Not for IV bolus administration.
- Do not mix or co-infuse CANCIDAS with other medications. Do not use diluents containing dextrose (α-D-glucose).

Adults [≥18 years of age] (2.2):

- Administer a single 70-mg loading dose on Day 1, followed by 50 mg once daily for all indications except esophageal candidiasis.
- For esophageal candidiasis, use 50 mg once daily with no loading dose.

Pediatric Patients [3 months to 17 years of age] (2.3):

- Dosing should be based on the patient's body surface area.
- For all indications, administer a single 70-mg/m^2 loading dose on Day 1, followed by 50 mg/m^2 once -daily thereafter.
- **Maximum loading dose and daily maintenance dose should not exceed 70 mg, regardless of the patient's calculated dose.**

Dosing With Rifampin and Other Inducers of Drug Clearance (2.5):

- Use 70 mg once daily dose ~~of CANCIDAS~~ for adult patients on rifampin.
- Consider dose increase to 70 mg ~~CANCIDAS~~ once daily for adult patients on nevirapine, efavirenz, carbamazepine, dexamethasone, or phenytoin.
- Pediatric patients receiving these same concomitant medications may also require an increase in dose to 70 mg/m^2 once daily (maximum daily dose not to exceed 70 mg).

The **DOSAGE FORMS AND STRENGTHS** section is revised as follows:

- Vials: 50 mg or 70 mg lyophylized powder (plus allowance for overfill) (3).
- ~~CANCIDAS 50 mg is a white to off-white /cake for infusion in a vial with a red aluminum band and a plastic cap. The vial contains 54.6 mg of caspofungin. (3)~~
- ~~CANCIDAS 70 mg is a white to off-white powder/cake for infusion in a vial with a yellow/orange aluminum band and a plastic cap. The vial contains 75.6 mg of caspofungin. (3)~~

The **WARNINGS AND PRECAUTIONS** section is revised as follows:

- ~~Concomitant u~~Use ~~of CANCIDAS~~ with cyclosporine: ~~should be l~~Limit~~ed~~ use to patients for whom ~~the~~ potential benefit outweighs ~~the~~ potential risk. ~~Patients~~ Monitor patients who develop abnormal liver function tests (LFTs) during concomitant therapy ~~should be monitored~~ and evaluate ~~the~~ risk/benefit of continuing CANCIDAS ~~therapy should be evaluated.~~ (5.1)
- ~~Abnormalities~~ Hepatic Effects: Can cause abnormalities in ~~liver function tests~~ LFTs and isolated cases of clinically significant hepatic dysfunction, hepatitis, ~~and~~ or hepatic failure ~~have been reported~~. ~~Patients~~ Monitor patients who develop abnormal ~~liver function tests~~ LFTs ~~during CANCIDAS therapy should be monitored~~ for evidence of worsening hepatic function and evaluated ~~for~~ risk/benefit of continuing CANCIDAS ~~therapy~~. (5.2)

The **ADVERSE REACTIONS** section is revised as follows:

- ~~Possible histamine-mediated symptoms have been reported. (6.1)~~
- Adults: Most common adverse reactions ~~for CANCIDAS~~ (incidence ≥10%) ~~in ADULTS:~~ are diarrhea, pyrexia, ~~chills,~~ ALT/AST increased, blood alkaline phosphatase increased, and blood potassium decreased. (6.1)
- Pediatric patients: Most common adverse reactions (incidence ≥10%) ~~in PEDIATRIC PATIENTS:~~ are pyrexia, diarrhea, rash, ALT/AST increased, blood potassium decreased, hypotension, and chills. (6.2)

The **USE IN SPECIFIC POPULATIONS** section is revised as follows:

- Pregnancy – Based on animal ~~No human~~ data, may cause. ~~Adverse effects in animals. Use if potential benefits of treatment outweigh potential~~ fetal harm ~~risk~~. (8.1)
- ~~Based upon pharmacokinetic data, a dosage reduction is recommended for adult patients with moderate hepatic insufficiency (35 mg daily, with a 70-mg loading dose on Day 1 where appropriate). (12.3)~~
- Pediatric use: Safety and efficacy ~~of CANCIDAS~~ in neonates and infants less than 3 months old has not been established. (8.4)
- Hepatic impairment: ~~Based upon pharmacokinetic data, a~~ Reduced dose~~age reduction is recommended~~ for adult patients with moderate hepatic impairment ~~insufficiency~~ (35 mg once daily, with a 70-mg loading dose on Day 1 where appropriate). No data are available in adults with severe impairment of in pediatric patients with any degree of impairment (8.6, 12.3)

(2) FULL PRESCRIBING INFORMATION:CONTENTS

Section **1 INDICATIONS AND USAGE** is revised as follows:

~~1.1~~ ●Empirical therapy for presumed fungal infections in febrile, neutropenic patients
~~1.2~~ ●Treatment of ~~C~~candidemia and the following *Candida* infections: intra-abdominal abscesses, peritonitis and pleural space infections
~~1.3~~ ●Treatment of e~~E~~sophageal c~~C~~andidiasis
~~1.4~~ ●Treatment of i~~I~~nvasive a~~A~~spergillosis in patients who are refractory to or intolerant of other therapies

Section **2 DOSAGE AND ADMINISTATION** is revised as follows:

2.4 Patients with Hepatic Impairment ~~Insufficiency~~

Section **5 WARNINGS AND PRECAUTIONS** is revised as follows:

~~5.3 Duration and Dose of CANCIDAS~~

Section **8 USE IN SPECIFIC POPULATIONS** is revised as follows:

8.6 Patients with Hepatic Impairment ~~Insufficiency~~
8.7 Patients with Renal Impairment ~~Insufficiency~~

(3) FULL PRESCRIBING INFORMATION

Section **2 DOSAGE AND ADMINISTRATION** is revised as follows**:**

In **2.1 Instructions for Use in All Patients**, the first sentence is revised as follows:

CANCIDAS should be administered by slow intravenous (IV) infusion ~~(IV)~~ over approximately 1 hour. CANCIDAS should not be administered by IV bolus administration.

In **2.2 Recommended Dosing in Adult Patients [≥18 years of age],** a new first paragraph is added, new subheadings are added, and other revisions are made as follows:

The usual dose is 50 mg once daily (following a 70-mg loading dose for most indications). The safety and efficacy of a dose of 150 mg daily (range: 1 to 51 days; median: 14 days) have been studied in 100 adult patients with candidemia and other *Candida* infections. The efficacy of CANCIDAS at this higher dose was not significantly better than the efficacy of the 50-mg daily dose of CANCIDAS. The efficacy of doses higher than 50 mg daily in the other adult patients for whom CANCIDAS is indicated is not known *[see Clinical Studies (14.2)*].

Empirical Therapy
A single 70-mg loading dose should be administered on Day 1, followed by 50 mg once daily thereafter. Duration of treatment should be based on the patient's clinical response. Empirical therapy should be continued until resolution of neutropenia. Patients found to have a fungal infection should be treated for a minimum of 14 days; treatment should continue for at least 7 days after both neutropenia and clinical symptoms are resolved. If the 50-mg dose is well tolerated but does not provide an adequate clinical response, the daily dose can be increased to 70 mg. ~~Although an increase in efficacy with 70 mg daily has not been demonstrated, limited safety data suggest that an increase in dose to 70 mg daily is well tolerated.~~

Candidemia and Other Candida Infections [see Clinical Studies (14.2)]
A single 70-mg loading dose should be administered on Day 1, followed by 50 mg once daily thereafter. Duration of treatment should be dictated by the patient's clinical and microbiological response. In general, antifungal therapy should continue for at least 14 days after the last positive culture. Patients who remain persistently neutropenic may warrant a longer course of therapy pending resolution of the neutropenia.

Esophageal Candidiasis
The dose is ~~should be~~ 50 mg once daily for 7 to 14 days after symptom resolution. A 70-mg loading dose has not been studied with this indication. Because of the risk of relapse of oropharyngeal candidiasis in patients with HIV infections, suppressive oral therapy could be considered *[see Clinical Studies (14.3)]*. ~~A 70-mg loading dose has not been studied with this indication.~~

Invasive Aspergillosis
A single 70-mg loading dose should be administered on Day 1, followed by 50 mg once daily thereafter. Duration of treatment should be based upon the severity of the patient's underlying disease, recovery from immunosuppression, and clinical response. ~~The efficacy of a 70-mg dose regimen in patients who are not clinically responding to the 50-mg daily dose is not known. Limited safety data suggest that an increase in dose to 70 mg daily is well tolerated. The safety and efficacy of doses above 70 mg have not been adequately studied.~~

In **2.3 Recommended Dosing in Pediatric Patients [3 months to 17 years of age]**, revisions are made to the first sentence and to the third paragraph. The second paragraph and formula are unchanged:

For all indications, a single 70-mg/m^2 loading dose should be administered on Day 1, followed by 50 mg/m^2 once daily thereafter.

Duration of treatment should be individualized to the indication, as described for each indication in adults *[see Dosage and Administration (2.2)]*. If the 50-mg/m^2 daily dose is well tolerated but does not provide an adequate clinical response, the daily dose can be increased to 70 mg/m^2 daily (not to exceed 70 mg). A~~lthough an increase in efficacy with 70-mg/m^2 daily has not been demonstrated, limited safety data suggest that an increase in dose to 70-mg/m^2 daily is well tolerated.~~

In **2.4 Patients with Hepatic Impairment ~~Insufficiency~~**, the following revisions are made:

Adult patients with mild hepatic impairment ~~insufficiency~~ (Child-Pugh score 5 to 6) do not need a dosage adjustment. For adult patients with moderate hepatic impairment ~~insufficiency~~ (Child-Pugh score 7 to 9), CANCIDAS 35 mg once daily is recommended based upon pharmacokinetic data *[see Clinical Pharmacology (12.3)]*. However, where recommended, a 70-mg loading dose should still be administered on Day 1. There is no clinical experience in adult patients with severe hepatic impairment ~~insufficiency~~ (Child-Pugh score >9) and in pediatric patients with any degree of hepatic impairment ~~insufficiency~~.

In **2.5 Patients Receiving Concomitant Inducers of Drug Clearance**, the following revisions are made:

Adult patients on rifampin should receive 70 mg of CANCIDAS once daily. Adult patients on nevirapine, efavirenz, carbamazepine, dexamethasone, or phenytoin may require an increase in dose to 70 mg of CANCIDAS once daily *[see Drug Interactions (7)]*.
When CANCIDAS is co-administered to pediatric patients with inducers of drug clearance, such as rifampin, efavirenz, nevirapine, phenytoin, dexamethasone, or carbamazepine, a CANCIDAS dose of 70 mg/m^2 once daily (not to exceed 70 mg) should be considered *[see Drug Interactions (7)]*.

In **2.6 Preparation and Reconstitution for Administration**, subheading names are updated, and editorial revisions are made:

~~***Preparation of CANCIDAS for Use***~~
Do not mix or co-infuse CANCIDAS with other medications, as there are no data available on the compatibility of CANCIDAS with other intravenous substances, additives, or medications. DO NOT USE DILUENTS CONTAINING DEXTROSE (α-D-GLUCOSE), as CANCIDAS is not stable in diluents containing dextrose.

[*remainder of section unchanged]*

Special Considerations for Pediatric Patients > 3 Months of Age

~~*[See Dosage and Administration (2.3).]*~~
Follow the reconstitution procedures described above using either the 70-mg or 50-mg vial to create the reconstituted solution *[See Dosage and Administration (2.3).]*

Section **4 CONTRAINDICATIONS** is revised as follows:

CANCIDAS is contraindicated in patients with hypersensitivity (e.g. anaphylaxis) to any component of this product *[see Adverse Reactions (6)]*.

Section **5 WARNINGS AND PRECAUTIONS** is revised as follows**:**

In **5.1 Concomitant Use with Cyclosporine**, the following text is added to the end of the first paragraph, and the first sentence of the second paragraph is also revised as follows:

In another clinical study, 2 of 8 healthy men developed transient ALT elevations of less than 2X ULN. In this study, cyclosporine (4 mg/kg) was administered on Days 1 and 12, and CANCIDAS was administered (70 mg) daily on Days 3 through 13. In one subject, the ALT elevation occurred on Days 7 and 9 and, in the other subject, the ALT elevation occurred on Day 19. These elevations returned to normal by Day 27. In all groups, elevations in AST paralleled ALT elevations but were of lesser magnitude. In these clinical studies, cyclosporine (one 4 mg/kg dose or two 3 mg/kg doses) increased the AUC of caspofungin by approximately 35%.

In a retrospective postmarketing study, 40 immunocompromised patients, including 37 transplant recipients, were treated ~~during marketed use~~ with CANCIDAS and cyclosporine for 1 to 290 days (median 17.5 days).

5.3 Duration and Dose of CANCIDAS is deleted in its entirety and replaced with information on the 150 mg dose in other parts of the package insert:

~~**5.3 Duration and Dose of CANCIDAS**~~

~~The efficacy of a 70-mg dose regimen in adult patients with invasive aspergillosis who are not clinically responding to the 50-mg daily dose is not known. Limited safety data suggest that an increase in dose to 70 mg daily is well tolerated. The safety and efficacy of doses above 70 mg have not been adequately studied in adult patients with *Candida* infections. However, CANCIDAS was generally well tolerated at a dose of 100 mg once daily for 21 days when administered to 15 adult healthy subjects.~~

~~The safety information on treatment durations longer than 4 weeks is limited in adult and pediatric patients; however, available data suggest that CANCIDAS continues to be well tolerated with longer courses of therapy (up to 162 days in adults and up to 87 days in pediatric patients).~~

Section **6 ADVERSE REACTIONS** is revised as follows:

A new first paragraph is added, and the sentences in the next paragraph are rearranged as follows:

The following serious adverse reactions are discussed in detail in another section of the labeling:

- Hepatic effects *[see Warnings and Precautions (5.2)]*

Anaphylaxis has been reported during administration of CANCIDAS. Possible histamine-mediated symptoms have been reported including reports of rash, facial swelling, pruritus, sensation of warmth, or bronchospasm. ~~Anaphylaxis has been reported during administration of CANCIDAS.~~

In **6.1 Clinical Trials Experience in Adults**, the first sentence is revised as follows:

The overall safety of CANCIDAS ~~caspofungin~~ was assessed in 1865~~661~~ adult individuals who received single or multiple doses of CANCIDAS ~~caspofungin acetate~~: 564 febrile, neutropenic patients (empirical therapy study); 382~~178~~ patients with candidemia and/or intra-abdominal abscesses, peritonitis, or pleural space infections (including 4 patients with chronic disseminated candidiasis); 297 patients with esophageal and/or oropharyngeal candidiasis; 228 patients with invasive aspergillosis; and 394 individuals in phase I studies.

In **6.1 Clinical Trials Experience in Adults**/*Empirical Therapy,* TABLE 2 and the text that follows are revised as follows:

TABLE 2
Adverse Reactions Among Patients with Persistent Fever and Neutropenia*
Incidence ≥7.5% for at Least One Treatment Group by System Organ Class or Preferred Term

Adverse Reaction (MedDRA v10.1 System Organ Class and Preferred Term)	CANCIDAS† N=564 (percent)	AmBisome‡ N=547 (percent)
All Systems, Any Adverse Reaction	**95.2**	**97.3**
~~**Cardiac Disorders**~~	~~**16.3**~~	~~**18.6**~~
~~Tachycardia~~	~~7.4~~	~~9.3~~
~~**Gastrointestinal Disorders**~~	~~**50.4**~~	~~**55.2**~~
~~Abdominal Pain~~	~~8.5~~	~~10.8~~
~~Diarrhea~~	~~20.2~~	~~15.9~~
~~Nausea~~	~~11.3~~	~~19.9~~
~~Vomiting~~	~~9.2~~	~~17.4~~
~~**General Disorders and Administration Site Conditions**~~	~~**57.1**~~	~~**63.3**~~

~~Chills~~	~~22.5~~	~~30.9~~
~~Mucosal Inflammation~~	~~6.0~~	~~7.5~~
~~Edema Peripheral~~	~~10.6~~	~~12.4~~
~~Pyrexia~~	~~27.1~~	~~29.1~~
~~Infections and Infestations~~	**~~44.9~~**	**~~42.0~~**
~~Pneumonia~~	~~11.3~~	~~9.9~~
~~Investigations~~	**~~57.6~~**	**~~63.1~~**
~~Alanine Aminotransferase Increased~~	~~18.1~~	~~20.1~~
~~Aspartate Aminotransferase Increased~~	~~14.2~~	~~17.4~~
~~Bilirubin Conjugated Increased~~	~~5.1~~	~~9.1~~
~~Blood Albumin Decreased~~	~~7.4~~	~~7.5~~
~~Blood Alkaline Phosphatase Increased~~	~~14.5~~	~~22.9~~
~~Blood Bilirubin Increased~~	~~10.3~~	~~13.7~~
~~Blood Creatinine Increased~~	~~3.4~~	~~11.3~~
~~Blood Glucose Increased~~	~~6.4~~	~~8.8~~
~~Blood Magnesium Decreased~~	~~7.1~~	~~9.0~~
~~Blood Potassium Decreased~~	~~15.2~~	~~22.5~~
~~Blood Urea Increased~~	~~3.9~~	~~7.9~~
~~Metabolism and Nutrition Disorders~~	**~~21.3~~**	**~~24.1~~**
~~Hypokalemia~~	~~6.4~~	~~8.2~~
~~Nervous System Disorders~~	**~~25.4~~**	**~~27.4~~**
~~Headache~~	~~10.5~~	~~12.1~~
~~Respiratory, Thoracic and Mediastinal Disorders~~	**~~46.5~~**	**~~48.8~~**
~~Cough~~	~~10.6~~	~~10.2~~
~~Dyspnea~~	~~9.2~~	~~9.7~~
~~Rales~~	~~6.9~~	~~7.7~~
~~Skin and Subcutaneous Tissue Disorders~~	**~~42.2~~**	**~~37.3~~**
~~Rash~~	~~16.0~~	~~13.5~~
~~Vascular Disorders~~	**~~19.5~~**	**~~23.0~~**
~~Hypotension~~	~~6.4~~	~~9.5~~

Investigations	**58**	**63**
Alanine Aminotransferase Increased	18	20
Blood Alkaline Phosphatase Increased	15	23
Blood Potassium Decreased	15	23
Aspartate Aminotransferase Increased	14	17
Blood Bilirubin Increased	10	14
Blood Albumin Decreased	7	8
Blood Magnesium Decreased	7	9
Blood Glucose Increased	6	9
Bilirubin Conjugated Increased	5	9
Blood Urea Increased	4	8
Blood Creatinine Increased	3	11
General Disorders and Administration Site Conditions	**57**	**63**
Pyrexia	27	29
Chills	23	31
Edema Peripheral	11	12
Mucosal Inflammation	6	8
Gastrointestinal Disorders	**50**	**55**
Diarrhea	20	16
Nausea	11	20
Abdominal Pain	9	11
Vomiting	9	17
Respiratory, Thoracic and Mediastinal Disorders	**47**	**49**
Cough	11	10
Dyspnea	9	10
Rales	7	8
Infections and Infestations	**45**	**42**
Pneumonia	11	10
Skin and Subcutaneous Tissue Disorders	**42**	**37**
Rash	16	14
Nervous System Disorders	**25**	**27**
Headache	11	12
Metabolism and Nutrition Disorders	**21**	**24**
Hypokalemia	6	8
Vascular Disorders	**20**	**23**
Hypotension	6	10

Cardiac Disorders	**16**	**19**
Tachycardia	7	9

Within any system organ class, individuals may experience more than 1 adverse reaction.
* Regardless of causality
† 70 mg on Day 1, then 50 mg once daily for the remainder of treatment; daily dose was increased to 70 mg for 73 patients.
‡ 3.0 mg/kg/day; daily dose was increased to 5.0 mg/kg for 74 patients.

The proportion of patients who experienced an infusion-related adverse reaction (~~defined An infusion-related adverse reaction was~~ defined as a systemic event, such as pyrexia, chills, flushing, hypotension, hypertension, tachycardia, dyspnea, tachypnea, rash, or anaphylaxis, that developed during the study therapy infusion and one hour following infusion) was significantly lower in the group treated with CANCIDAS (35.~~1~~%) than in the group treated with AmBisome (52~~51.6~~%).

To evaluate the effect of CANCIDAS and AmBisome on renal function, nephrotoxicity was defined as doubling of serum creatinine relative to baseline or an increase of ≥1 mg/dL in serum creatinine if baseline serum creatinine was above the upper limit of the normal range. Among patients whose baseline creatinine clearance was >30 mL/min, the incidence of nephrotoxicity was significantly lower in the group treated with CANCIDAS (3~~2.6~~%) than in the group treated with AmBisome (12~~11.5~~%). Clinical renal events, regardless of causality, were similar between CANCIDAS (75/564, 13.~~3~~%) and AmBisome (85/547, 116~~115.5~~%).

In **6.1 Clinical Trials Experience in Adults/***Candidemia and Other Candida Infections*, TABLE 3 and the text that follows are revised. New information regarding the 150 mg CANCIDAS dose and a new TABLE 4 are added:

TABLE 3
Adverse Reactions Among Patients with Candidemia or other *Candida* Infections*,†
Incidence ≥10% for at Least One Treatment Group by System Organ Class or Preferred Term

Adverse Reaction (MedDRA v10.1 System Organ Class and Preferred Term)	CANCIDAS 50 mg‡ N=114 (percent)	Amphotericin B N=125 (percent)
All Systems, Any Adverse Reaction	**9695.6**	**99.2**
~~Blood and Lymphatic System Disorders~~	**~~14.9~~**	**~~12.8~~**
~~Anemia~~	~~10.5~~	~~8.8~~
~~Cardiac Disorders~~	**~~26.3~~**	**~~33.6~~**
~~Tachycardia~~	~~7.9~~	~~12.0~~
~~Gastrointestinal Disorders~~	**~~49.1~~**	**~~52.8~~**
~~Diarrhea~~	~~14.0~~	~~10.4~~
~~Nausea~~	~~8.8~~	~~16.8~~
~~Vomiting~~	~~16.7~~	~~16.0~~
~~General Disorders and Administration Site Conditions~~	**~~46.5~~**	**~~63.2~~**
~~Chills~~	~~8.8~~	~~29.6~~
~~Edema Peripheral~~	~~10.5~~	~~12.0~~
~~Pyrexia~~	~~13.2~~	~~32.8~~
~~Infections and Infestations~~	**~~48.2~~**	**~~53.6~~**
~~Pneumonia~~	~~4.4~~	~~10.4~~
~~Septic Shock~~	~~10.5~~	~~8.8~~
~~Investigations~~	**~~66.7~~**	**~~81.6~~**
~~Alanine Aminotransferase Increased~~	~~15.8~~	~~15.2~~
~~Aspartate Aminotransferase Increased~~	~~15.8~~	~~14.4~~
~~Bilirubin Conjugated Increased~~	~~7.9~~	~~13.6~~
~~Blood Alkaline Phosphatase Increased~~	~~21.1~~	~~32.0~~
~~Blood Bilirubin Increased~~	~~13.2~~	~~16.8~~
~~Blood Creatinine Increased~~	~~11.4~~	~~28.0~~
~~Blood Potassium Decreased~~	~~22.8~~	~~32.0~~
~~Blood Urea Increased~~	~~8.8~~	~~23.2~~
~~Hematocrit Decreased~~	~~13.2~~	~~18.4~~
~~Hemoglobin Decreased~~	~~18.4~~	~~23.2~~
~~Red Blood Cells Urine Positive~~	~~9.6~~	~~10.4~~
~~Respiratory, Thoracic and Mediastinal Disorders~~	**~~39.5~~**	**~~53.6~~**

~~Pleural Effusion~~	~~8.8~~	~~14.4~~
~~Respiratory Failure~~	~~10.5~~	~~12.0~~
~~Tachypnea~~	~~0.9~~	~~11.2~~
~~**Skin and Subcutaneous Tissue Disorders**~~	~~**25.4**~~	~~**28.0**~~
~~Rash~~	~~3.5~~	~~10.4~~
~~**Vascular Disorders**~~	~~**24.6**~~	~~**37.6**~~
~~Hypotension~~	~~9.6~~	~~16.0~~

Investigations	**67**	**82**
Blood Potassium Decreased	23	32
Blood Alkaline Phosphatase Increased	21	32
Hemoglobin Decreased	18	23
Alanine Aminotransferase Increased	16	15
Aspartate Aminotransferase Increased	16	14
Blood Bilirubin Increased	13	17
Hematocrit Decreased	13	18
Blood Creatinine Increased	11	28
Red Blood Cells Urine Positive	10	10
Blood Urea Increased	9	23
Bilirubin Conjugated Increased	8	14
Gastrointestinal Disorders	**49**	**53**
Vomiting	17	16
Diarrhea	14	10
Nausea	9	17
Infections and Infestations	**48**	**54**
Septic Shock	11	9
Pneumonia	4	10
General Disorders and Administration Site Conditions	**47**	**63**
Pyrexia	13	33
Edema Peripheral	11	12
Chills	9	30
Respiratory, Thoracic and Mediastinal Disorders	**40**	**54**
Respiratory Failure	11	12
Pleural Effusion	9	14
Tachypnea	1	11
Cardiac Disorders	**26**	**34**
Tachycardia	8	12
Skin and Subcutaneous Tissue Disorders	**25**	**28**
Rash	4	10
Vascular Disorders	**25**	**38**
Hypotension	10	16
Blood and Lymphatic System Disorders	**15**	**13**
Anemia	11	9

Within any system organ class, individuals may experience more than 1 adverse reaction.
* Intra-abdominal abscesses, peritonitis and pleural space infections.
† Regardless of causality
‡ Patients received CANCIDAS 70 mg on Day 1, then 50 mg once daily for the remainder of their treatment.

The proportion of patients who experienced an infusion-related adverse reaction (~~An infusion-related adverse reaction was~~ defined as a systemic event, such as pyrexia, chills, flushing, hypotension, hypertension, tachycardia, dyspnea, tachypnea, rash, or anaphylaxis, that developed during the study therapy infusion and one hour following infusion) was significantly lower in the group treated with CANCIDAS (20.~~2~~%) than in the group treated with amphotericin B (49~~8.8~~%).

[new information, including Table 4]
In a second randomized, double-blinded invasive candidiasis study, patients received either CANCIDAS 50 mg/day (following a 70-mg loading dose) or CANCIDAS 150 mg/day. The proportion of patients who experienced any adverse reaction was similar in the 2 treatment groups; however, this study was not large enough to detect differences in rare or unexpected adverse events. Adverse reactions occurring in ≥5% of the patients in either treatment group are presented in Table 4.

TABLE 4
Adverse Reactions Among Patients with Candidemia or other *Candida* Infections*, †
Incidence ≥5% for at Least One Treatment Group by System Organ Class or Preferred Term

Adverse Reaction (MedDRA v11.0 System Organ Class and Preferred Term)	CANCIDAS 50 mg‡ N=104 (percent)	CANCIDAS 150 mg N=100 (percent)
All Systems, Any Adverse Reaction	**83**	**83**
Infections and Infestations	**44**	**43**
Septic Shock	13	14
Pneumonia	5	7
Sepsis	5	7
General Disorders and Administration Site Conditions	**33**	**27**
Pyrexia	6	6
Gastrointestinal Disorders	**30**	**33**
Vomiting	11	6
Diarrhea	6	7
Nausea	5	7
Investigations	**28**	**35**
Alkaline Phosphatase Increased	12	9
Aspartate Aminotransferase Increased	6	9
Blood potassium decreased	6	8
Alanine Aminotransferase Increased	4	7
Respiratory, Thoracic and Mediastinal Disorders	**23**	**26**
Respiratory Failure	6	2
Vascular Disorders	**19**	**18**
Hypotension	7	3
Hypertension	5	6
Skin and Subcutaneous Tissue Disorders	**15**	**15**
Decubitus Ulcer	3	5

Within any system organ class, individuals may experience more than 1 adverse event
* Intra-abdominal abscesses, peritonitis and pleural space infections.
† Regardless of causality
‡ Patients received CANCIDAS 70 mg on Day 1, then 50 mg once daily for the remainder of their treatment.

In **6.1 Clinical Trials Experience in Adults/** *Esophageal Candidiasis and Oropharyngeal Candidiasis*, TABLE 4 is renumbered TABLE 5 and the contents are revised as follows:

~~**TABLE 4**~~
~~**Adverse Reactions Among Patients with Esophageal and/or Oropharyngeal Candidiasis***~~
~~Incidence ≥10% for at Least One Treatment Group by System Organ Class or Preferred Term~~

~~Adverse Reaction (MedDRA v10.1 System Organ Class and Preferred Term)~~	~~CANCIDAS 50 mg† N=83 (percent)~~	~~Fluconazole IV 200 mg† N=94 (percent)~~
~~**All Systems, Any Adverse Reaction**~~	~~**90.4**~~	~~**92.6**~~
~~**Gastrointestinal Disorders**~~	~~**57.8**~~	~~**50.0**~~
~~Diarrhea~~	~~26.5~~	~~18.1~~
~~Nausea~~	~~14.5~~	~~14.9~~
~~**General Disorders and Administration Site Conditions**~~	~~**31.3**~~	~~**36.2**~~
~~Pyrexia~~	~~20.5~~	~~21.3~~
~~**Investigations**~~	~~**53.0**~~	~~**60.6**~~
~~Alanine Aminotransferase Increased~~	~~12.0~~	~~17.0~~
~~Aspartate Aminotransferase Increased~~	~~13.3~~	~~19.1~~
~~Blood Alkaline Phosphatase Increased~~	~~13.3~~	~~17.0~~
~~Hematocrit Decreased~~	~~18.1~~	~~16.0~~
~~Hemoglobin Decreased~~	~~20.5~~	~~16.0~~
~~White Blood Cell Count Decreased~~	~~12.0~~	~~19.1~~
~~**Nervous System Disorders**~~	~~**18.1**~~	~~**17.0**~~
~~Headache~~	~~14.5~~	~~8.5~~
~~**Vascular Disorders**~~	~~**19.3**~~	~~**14.9**~~
~~Phlebitis~~	~~18.1~~	~~10.6~~

TABLE 5
Adverse Reactions Among Patients with Esophageal and/or Oropharyngeal Candidiasis*
Incidence ≥10% for at Least One Treatment Group by System Organ Class or Preferred Term

Adverse Reaction (MedDRA v10.1 System Organ Class and Preferred Term)	CANCIDAS 50 mg† N=83 (percent)	Fluconazole IV 200 mg† N=94 (percent)
All Systems, Any Adverse Reaction	90	93
Gastrointestinal Disorders	58	50
Diarrhea	27	18
Nausea	15	15
Investigations	53	61
Hemoglobin Decreased	21	16
Hematocrit Decreased	18	16
Aspartate Aminotransferase Increased	13	19
Blood Alkaline Phosphatase Increased	13	17
Alanine Aminotransferase Increased	12	17
White Blood Cell Count Decreased	12	19
General Disorders and Administration Site Conditions	31	36
Pyrexia	21	21
Vascular Disorders	19	15
Phlebitis	18	11
Nervous System Disorders	18	17
Headache	15	9

Within any system organ class, individuals may experience more than 1 adverse reaction.
*Regardless of causality
†Derived from a ~~Phase III~~ comparator-controlled clinical study.

In **6.1 Clinical Trials Experience in Adult/** *Invasive Aspergillosis*, the first paragraph is revised and the second paragraph is deleted in its entirety:

Invasive Aspergillosis
In an open-label, noncomparative aspergillosis study, in which 69 patients received CANCIDAS (70-mg loading dose on Day 1 followed by 50 mg daily), the following treatment-emergent adverse reactions were observed with an incidence of ≥12.5%: blood alkaline phosphatase increased (22~~1.7~~%), hypotension (20.~~3~~%), respiratory failure (20.~~3~~%), pyrexia (17~~17.4~~%), diarrhea (15~~4.5~~%), nausea (15~~4.5~~%), headache (15~~4.5~~%), rash (13.0%), aspergillosis (13.0%), alanine aminotransferase increased (13.0%), aspartate aminotransferase increased (13.0%), blood bilirubin increased (13.0%), and blood potassium decreased (13.0%). Also reported infrequently in this patient population were pulmonary edema, ARDS (adult respiratory distress syndrome), and radiographic infiltrates.

~~*Concomitant Therapy*~~
~~In one clinical study, 3 of 4 adult subjects who received CANCIDAS 70 mg daily on Days 1 through 10, and also received two 3 mg/kg doses of cyclosporine 12 hours apart on Day 10, developed transient elevations of ALT on Day 11 that were 2 to 3 times the upper limit of normal (ULN). In a separate panel of adult subjects in the same study, 2 of 8 subjects who received CANCIDAS 35 mg daily for 3 days and cyclosporine (two 3 mg/kg doses administered 12 hours apart) on Day 1 had small increases in ALT (slightly above the ULN) on Day 2. In another clinical study, 2 of 8 healthy men developed transient ALT elevations of less than 2X ULN. In this study, cyclosporine (4 mg/kg) was administered on Days 1 and 12, and CANCIDAS was administered (70 mg) daily on Days 3 through 13. In one subject, the ALT elevation occurred on Days 7 and 9 and, in the other subject, the ALT elevation occurred on Day 19. These elevations returned to normal by Day 27. In all groups, elevations~~

~~in AST paralleled ALT elevations but were of lesser magnitude. In these clinical studies, cyclosporine (one 4 mg/kg dose or two 3 mg/kg doses) increased the AUC of caspofungin by approximately 35% *[see Warnings and Precautions (5.1)].*~~

In **6.2 Clinical Trials Experience in Pediatric Patients (3 months to 17 years of age)**, the first sentence in the first paragraph, and second paragraphs are revised, and TABLE 5 is renumbered TABLE 6 and revised as follows:

The overall safety of CANCIDAS ~~caspofungin~~ was assessed in 171 pediatric patients who received single or multiple doses of CANCIDAS.

One patient (0.6%) receiving CANCIDAS, and three patients (12~~1.5~~%) receiving AmBisome developed a serious drug-related adverse reaction. Two patients (1.~~2~~%) were discontinued from CANCIDAS and three patients (12~~1.5~~%) were discontinued from AmBisome due to a drug-related adverse reaction. The proportion of patients who experienced an infusion-related adverse reaction (defined as a systemic event, such as pyrexia, chills, flushing, hypotension, hypertension, tachycardia, dyspnea, tachypnea, rash, or anaphylaxis, that developed during the study therapy infusion and one hour following infusion) was 22~~1.6~~% in the group treated with CANCIDAS and 35~~4.6~~% in the group treated with AmBisome.

TABLE 6~~5~~

Adverse Reactions Among Pediatric Patients (0 months to 17 years of age)*

Incidence ≥7.5% for at Least One Treatment Group by System Organ Class or Preferred Term

Adverse Reaction (MedDRA v10.0 System Organ Class and Preferred Term)	Noncomparative Clinical Studies: CANCIDAS Any Dose N=115 (percent)	Comparator-Controlled Clinical Study of Empirical Therapy: CANCIDAS 50 mg/m^2† N=56 (percent)	Comparator-Controlled Clinical Study of Empirical Therapy: AmBisome 3 mg/kg N=26 (percent)
All Systems, Any Adverse Reaction	**95~~4.8~~**	**96.4**	**89~~8.5~~**
~~Blood and Lymphatic System Disorders~~	**~~10.4~~**	**~~1.8~~**	**~~15.4~~**
~~Anemia~~	~~1.7~~	~~0.0~~	~~7.7~~
~~Cardiac Disorders~~	**~~17.4~~**	**~~12.5~~**	**~~19.2~~**
~~Tachycardia~~	~~3.5~~	~~10.7~~	~~19.2~~
~~Gastrointestinal Disorders~~	**~~41.7~~**	**~~41.1~~**	**~~34.6~~**
~~Abdominal Pain~~	~~7.0~~	~~3.6~~	~~11.5~~
~~Diarrhea~~	~~17.4~~	~~7.1~~	~~15.4~~
~~Nausea~~	~~3.5~~	~~3.6~~	~~7.7~~
~~Vomiting~~	~~7.8~~	~~10.7~~	~~11.5~~
~~General Disorders and Administration Site Conditions~~	**~~47.0~~**	**~~58.9~~**	**~~42.3~~**
~~Chills~~	~~10.4~~	~~12.5~~	~~7.7~~
~~Edema~~	~~2.6~~	~~3.6~~	~~7.7~~
~~Mucosal Inflammation~~	~~10.4~~	~~3.6~~	~~3.8~~
~~Pyrexia~~	~~28.7~~	~~30.4~~	~~23.1~~
~~Immune System Disorders~~	**~~7.0~~**	**~~7.1~~**	**~~11.5~~**
~~Graft Versus Host Disease~~	~~0.9~~	~~3.6~~	~~7.7~~
~~Infections and Infestations~~	**~~40.0~~**	**~~30.4~~**	**~~34.6~~**
~~Central Line Infection~~	~~0.9~~	~~8.9~~	~~0.0~~
~~Investigations~~	**~~54.8~~**	**~~41.1~~**	**~~50.0~~**
~~Alanine Aminotransferase Increased~~	~~13.9~~	~~5.4~~	~~11.5~~
~~Aspartate Aminotransferase Increased~~	~~16.5~~	~~1.8~~	~~11.5~~
~~Blood Potassium Decreased~~	~~18.3~~	~~8.9~~	~~26.9~~
~~Blood Potassium Increased~~	~~2.6~~	~~0.0~~	~~7.7~~
~~Protein Total Decreased~~	~~0.0~~	~~0.0~~	~~7.7~~
~~Metabolism and Nutrition Disorders~~	**~~21.7~~**	**~~10.7~~**	**~~23.1~~**
~~Hypokalemia~~	~~7.8~~	~~5.4~~	~~3.8~~
~~Musculoskeletal and Connective Tissue Disorders~~	**~~11.3~~**	**~~14.3~~**	**~~11.5~~**
~~Back Pain~~	~~3.5~~	~~0.0~~	~~7.7~~
~~Nervous System Disorders~~	**~~13.0~~**	**~~16.1~~**	**~~7.7~~**
~~Headache~~	~~5.2~~	~~8.9~~	~~3.8~~
~~Respiratory, Thoracic and Mediastinal Disorders~~	**~~42.6~~**	**~~32.1~~**	**~~26.9~~**
~~Cough~~	~~6.1~~	~~8.9~~	~~7.7~~
~~Respiratory Distress~~	~~7.8~~	~~0.0~~	~~3.8~~
~~Skin and Subcutaneous Tissue Disorders~~	**~~33.0~~**	**~~41.1~~**	**~~38.5~~**
~~Erythema~~	~~3.5~~	~~8.9~~	~~0.0~~
~~Pruritus~~	~~7.0~~	~~5.4~~	~~7.7~~
~~Rash~~	~~6.1~~	~~23.2~~	~~7.7~~

~~Vascular Disorders~~	~~24.3~~	~~21.4~~	~~19.2~~
~~Hypertension~~	~~9.6~~	~~8.9~~	~~3.8~~
~~Hypotension~~	~~12.2~~	~~8.9~~	~~7.7~~

Investigations	55	41	50
Blood Potassium Decreased	18	9	27
Aspartate Aminotransferase Increased	17	2	12
Alanine Aminotransferase Increased	14	5	12
Blood Potassium Increased	3	0	8
Protein Total Decreased	0	0	8
General Disorders and Administration Site Conditions	47	59	42
Pyrexia	29	30	23
Chills	10	13	8
Mucosal Inflammation	10	4	4
Edema	3	4	8
Respiratory, Thoracic and Mediastinal Disorders	43	32	27
Respiratory Distress	8	0	4
Cough	6	9	8
Gastrointestinal Disorders	42	41	35
Diarrhea	17	7	15
Vomiting	8	11	12
Abdominal Pain	7	4	12
Nausea	4	4	8
Infections and Infestations	40	30	35
Central Line Infection	1	9	0
Skin and Subcutaneous Tissue Disorders	33	41	39
Pruritus	7	6	8
Rash	6	23	8
Erythema	4	9	0
Vascular Disorders	24	21	19
Hypotension	12	9	8
Hypertension	10	9	4
Metabolism and Nutrition Disorders	22	11	23
Hypokalemia	8	5	4
Cardiac Disorders	17	13	19
Tachycardia	4	11	19
Nervous System Disorders	13	16	8
Headache	5	9	4
Musculoskeletal and Connective Tissue Disorders	11	14	12
Back Pain	4	0	8
Blood and Lymphatic System Disorders	10	2	15
Anemia	2	0	8
Immune System Disorders	7	7	12
Graft Versus Host Disease	1	4	8

Within any system organ class, individuals may experience more than 1 adverse reaction.
* Regardless of causality
† 70 mg/m^2 on Day 1, then 50 mg/m^2 once daily for the remainder of the treatment.

In **6.3 Overall Safety Experience of CANCIDAS in Clinical Trials**, the first and second paragraphs are revised, and TABLE 6 is renumbered TABLE 7 and revised as follows:

The overall safety of CANCIDAS was assessed in ~~1832~~ 2036 individuals (including ~~1438~~ 1642 adult or pediatric patients and 394 volunteers) from ~~33~~ 34 clinical studies. These individuals received single or multiple (once daily) doses of CANCIDAS, ranging from 5 mg to 210 mg. Full safety data is available from ~~1747~~ 1951 individuals, as the safety data from 85 patients enrolled in 2 compassionate use studies was limited solely to serious adverse reactions. Treatment emergent adverse reactions, regardless of causality, which occurred in ≥5% of all individuals who received CANCIDAS in these trials, are shown in Table ~~6~~ 7.

Overall, ~~1496~~ 1665 of the ~~1747~~ 1951 (~~85.6~~ 85%) patients/volunteers who received CANCIDAS experienced an adverse reaction.

TABLE ~~7~~6

Treatment-Emergent* Adverse Reactions in Patients Who Received CANCIDAS in Clinical Trials†
Incidence ≥5% for at Least One Treatment Group by System Organ Class or Preferred Term

Adverse Reaction‡ (MedDRA v10 System Organ Class and Preferred Term)	CANCIDAS (N = 1951~~747~~)	
	n	(%)
All Systems, Any Adverse Reaction	**1665~~496~~**	**(85.~~6~~)**
~~**Gastrointestinal Disorders**~~	~~**690**~~	~~**(39.5)**~~
~~Abdominal Pain~~	~~109~~	~~(6.2)~~
~~Diarrhea~~	~~260~~	~~(14.9)~~
~~Nausea~~	~~154~~	~~(8.8)~~
~~Vomiting~~	~~129~~	~~(7.4)~~
~~**General Disorders and Administration Site Conditions**~~	~~**782**~~	~~**(44.8)**~~
~~Chills~~	~~191~~	~~(10.9)~~
~~Edema Peripheral~~	~~104~~	~~(6.0)~~
~~Pyrexia~~	~~369~~	~~(21.1)~~
~~**Infections and Infestations**~~	~~**641**~~	~~**(36.7)**~~
~~Pneumonia~~	~~103~~	~~(5.9)~~
~~**Investigations**~~	~~**835**~~	~~**(47.8)**~~
~~Alanine Aminotransferase Increased~~	~~247~~	~~(14.1)~~
~~Aspartate Aminotransferase Increased~~	~~218~~	~~(12.5)~~
~~Blood Alkaline Phosphatase Increased~~	~~211~~	~~(12.1)~~
~~Blood Bilirubin Increased~~	~~111~~	~~(6.4)~~
~~Blood Potassium Decreased~~	~~206~~	~~(11.8)~~
~~Hemoglobin Decreased~~	~~95~~	~~(5.4)~~
~~**Nervous System Disorders**~~	~~**387**~~	~~**(22.2)**~~
~~Headache~~	~~184~~	~~(10.5)~~
~~**Respiratory, Thoracic, and Mediastinal Disorders**~~	~~**563**~~	~~**(32.2)**~~
~~Cough~~	~~110~~	~~(6.3)~~
~~**Skin and Subcutaneous Tissue Disorders**~~	~~**489**~~	~~**(28.0)**~~
~~Erythema~~	~~95~~	~~(5.4)~~
~~Rash~~	~~151~~	~~(8.6)~~
~~**Vascular Disorders**~~	~~**306**~~	~~**(17.5)**~~
~~Hypotension~~	~~108~~	~~(6.2)~~

Investigations	**901**	**(46)**
Alanine Aminotransferase Increased	258	(13)
Aspartate Aminotransferase Increased	233	(12)
Blood Alkaline Phosphatase Increased	232	(12)
Blood Potassium Decreased	220	(11)
Blood Bilirubin Increased	117	(6)
General Disorders and Administration Site Conditions	**843**	**(43)**
Pyrexia	381	(20)
Chills	192	(10)
Edema Peripheral	110	(6)
Gastrointestinal Disorders	**754**	**(39)**
Diarrhea	273	(14)
Nausea	166	(9)
Vomiting	146	(8)
Abdominal Pain	112	(6)
Infections and Infestations	**730**	**(37)**
Pneumonia	115	(6)
Respiratory, Thoracic, and Mediastinal Disorders	**613**	**(31)**
Cough	111	(6)
Skin and Subcutaneous Tissue Disorders	**520**	**(27)**
Rash	159	(8)
Erythema	98	(5)
Nervous System Disorders	**412**	**(21)**
Headache	193	(10)
Vascular Disorders	**344**	**(18)**
Hypotension	118	(6)

* Defined as an adverse reaction, regardless of causality, while on CANCIDAS or during the 14-day post-CANCIDAS follow-up period.
† Incidence for each preferred term is ≥5% among individuals who received at least 1 dose of CANCIDAS.
‡ Within any system organ class, individuals may experience more than 1 adverse event.

Clinically significant adverse reactions, regardless of causality or incidence which occurred in ~~these trials,~~ less than 5% of patients are listed below.

In **6.4 Postmarketing Experience**, the first sentence is revised as follows:

The following additional adverse reactions have been identified during the post-approval use of CANCIDAS ~~caspofungin~~.

Section **7 DRUG INTERACTIONS**: The *Cyclosporine* subsection is relocated and placed ahead of the *Tacrolimus* subsection.

Section **8 USE IN SPECIFIC POPULATIONS** is revised as follows**:**

In **8.4 Pediatric Use**, the last paragraph is modified as follows:

In clinical trials, 171 pediatric patients (0 months to 17 years of age), including 18 patients who were less than 3 months of age, were given intravenous CANCIDAS. Pharmacokinetic studies enrolled a total of 66 pediatric patients, and an additional 105 pediatric patients received CANCIDAS in safety and efficacy studies. *[See Clinical Studies (14.5).]* The majority of the pediatric patients received CANCIDAS at a once-daily maintenance dose of 50 mg/m^2 for a mean duration of 12 days (median 9, range 1-87 days). In all studies, safety was assessed by the investigator throughout study therapy and for 14 days following cessation of study therapy. The most common adverse reactions in pediatric patients treated with CANCIDAS were pyrexia (29~~.2~~%), blood potassium decreased (15~~.2~~%), diarrhea (14%), increased aspartate aminotransferase (12~~1.7~~%), rash (12~~1.7~~%), increased alanine aminotransferase (11~~.1~~%), hypotension (11~~.1~~%), and chills (1~~1.1~~%). *[See Adverse Reactions (6.2).]*

In **8.6 Patients with Hepatic Insufficiency**, the header and text are revised as follows:

8.6 Patients with Hepatic Impairment ~~Insufficiency~~
Adult patients with mild hepatic impairment ~~insufficiency~~ (Child-Pugh score 5 to 6) do not need a dosage adjustment. For adult patients with moderate hepatic impairment ~~insufficiency~~ (Child-Pugh score 7 to 9), CANCIDAS 35 mg once daily is recommended based upon pharmacokinetic data *[see Clinical Pharmacology (12.3)]*. However, where recommended, a 70-mg loading dose should still be administered on Day 1 *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*. There is no clinical experience in adult patients with severe hepatic impairment ~~insufficiency~~ (Child-Pugh score >9) and in pediatric patients 3 months to 17 years of age with any degree of hepatic impairment ~~insufficiency~~.

In **8.7 Patients with Renal Insufficiency**, the header and text are revised as follows:

8.7 Patients with Renal Impairment ~~Insufficiency~~
No dosage adjustment is necessary for patients with renal impairment ~~insufficiency~~. Caspofungin is not dialyzable; thus, supplementary dosing is not required following hemodialysis *[see Clinical Pharmacology (12.3)]*.

Section **10 OVERDOSAGE** is revised as follows:

In ~~adult clinical studies the highest dose was 210 mg, administered as single dose to~~ 6 healthy subjects ~~This dose was generally well tolerated. In addition, 100 mg once~~ who received a single 210 mg dose, no significant adverse reactions were reported. Multiple doses above 150 mg daily ~~for 21 days has~~ have not been ~~administered to 15 healthy subjects and was generally well toleraded~~ studied. Caspofungin is not dialyzable. The minimum lethal dose of caspofungin in rats was 50 mg/kg, a dose which is equivalent to 10 times the recommended daily dose based on relative body surface area comparison.
In clinical trials, one pediatric patient (16 years of age) unintentionally received a single dose of caspofungin of 113 mg (on Day 1), followed by 80 mg daily for an additional 7 days. ~~These dosages were generally well tolerated~~. No clinically significant adverse reactions were reported.

Section **11 DESCRIPTION**, the first paragraph is revised as follows:

CANCIDAS is a sterile, lyophilized product for intravenous (IV) infusion that contains a semisynthetic lipopeptide (echinocandin) compound synthesized from a fermentation product of *Glarea lozoyensis.* CANCIDAS is ~~the first of a new class of antifungal drugs~~ an echinocandin~~s~~ that inhibits the synthesis of β (1,3)-D-glucan, an integral component of the fungal cell wall.

Section **12 CLINICAL PHARMACOLOGY** is revised as follows**:**

12.1 Mechanism of Action is revised as follows:

Caspofungin ~~acetate, an echinocandins,~~ is an antifungal ~~agent~~ drug *[see Clinical Pharmacology (12.4)]*.

In **12.3 Pharmacokinetics,** a new sentence is added at the beginning of the subsection:

Adult and pediatric pharmacokinetic parameters are presented in Table 8.

In **12.3 Pharmacokinetics/*Special Populations,*** the headers and sections for the *Renal Insufficiency* and *Hepatic Insufficiency* are revised as shown below. In addition, the *Race* subsection is repositioned to follow the *Gender* subsection.

Renal Impairment ~~*Insufficiency*~~
In a clinical study of single 70-mg doses, caspofungin pharmacokinetics were similar in healthy adult volunteers with mild renal impairment ~~insufficiency~~ (creatinine clearance 50 to 80 mL/min) and control subjects. Moderate (creatinine clearance 31 to 49 mL/min), severe ~~advanced~~ (creatinine clearance 5 to 30 mL/min), and end-stage (creatinine clearance <10 mL/min and dialysis dependent) renal impairment ~~insufficiency~~ moderately increased caspofungin plasma concentrations after single-dose administration (range: 30 to 49% for AUC). However, in adult patients with invasive aspergillosis, candidemia, or other *Candida* infections (intra-abdominal abscesses, peritonitis, or pleural space infections) who received multiple daily doses of CANCIDAS 50 mg, there was no significant effect of mild to end-stage renal impairment on caspofungin concentrations. No dosage adjustment is

necessary for patients with renal impairment ~~insufficiency~~. Caspofungin is not dialyzable, thus supplementary dosing is not required following hemodialysis.

Hepatic Impairment ~~Insufficiency~~
Plasma concentrations of caspofungin after a single 70-mg dose in adult patients with mild hepatic impairment ~~insufficiency~~ (Child-Pugh score 5 to 6) were increased by approximately 55% in AUC compared to healthy control subjects. In a 14-day multiple-dose study (70 mg on Day 1 followed by 50 mg daily thereafter), plasma concentrations in adult patients with mild hepatic impairment ~~insufficiency~~ were increased modestly (19 to 25% in AUC) on Days 7 and 14 relative to healthy control subjects. No dosage adjustment is recommended for patients with mild hepatic impairment ~~insufficiency~~. Adult patients with moderate hepatic impairment ~~insufficiency~~ (Child-Pugh score 7 to 9) who received a single 70-mg dose of CANCIDAS had an average plasma caspofungin increase of 76% in AUC compared to control subjects. A dosage reduction is recommended for adult patients with moderate hepatic impairment ~~insufficiency~~ based upon these ~~is~~ pharmacokinetic data *[see Dosage and Administration (2.4)]*. There is no clinical experience in adult patients with severe hepatic impairment ~~insufficiency~~ (Child-Pugh score >9) or in pediatric patients with any degree of hepatic impairment ~~insufficiency~~.

In **12.3 Pharmacokinetics/***Drug Interactions,* the *Cyclosporine* subsection is moved to be located above the *Tacrolimus* subsection.

In **12.4 Microbiology**/*Mechanism of action* subsection, the fist sentence is revised as follows:

Caspofungin ~~acetate, the active ingredient of CANCIDAS~~, an echinocandin, inhibits the synthesis of β (1,3)-D-glucan, an essential component of the cell wall of susceptible *Aspergillus* species and *Candida* species. β (1,3)-D-glucan is not present in mammalian cells.

Section **14 CLINICAL STUDIES** is revised as follows**.**

In **14.2 Candidemia and the Following other Candida Infections**, the footer for TABLE 12 is revised to read “then 50 mg once daily;” in addition, the following new paragraph regarding the 150 mg CANCIDAS study is added at the end of the subsection:

In a second randomized, double-blind study, 197 patients with proven invasive candidiasis received CANCIDAS 50 mg/day (following a 70-mg loading dose on Day 1) or CANCIDAS 150 mg/day. The diagnostic criteria, evaluation time points, and efficacy endpoints were similar to those employed in the prior study. Patients with *Candida* endocarditis, meningitis, or osteomyelitis were excluded. Although this study was designed to compare the safety of the two doses, it was not large enough to detect differences in rare or unexpected adverse events *[see Adverse Reactions (6.1)]*. A significant improvement in efficacy with the 150-mg daily dose was not seen when compared to the 50-mg dose.

In **14.3 Esophageal Candidiasis (and information on oropharyngeal candidiasis),** the text below the TABLE 16 is moved up, and TABLE 15 and TABLE 16 are merged to create a single revised TABLE 16 as follows:

~~**TABLE 15**~~
~~**Oropharyngeal Candidiasis Response Rates at 5 to 7 Days Post-Therapy in Patients with Oropharyngeal and Esophageal Candidiasis at Baseline**~~

	~~CANCIDAS~~	~~Fluconazole~~	~~% Difference* (95% CI)~~
~~Day 5-7 post-treatment~~	~~40/56 (71.4%)~~	~~55/66 (83.3%)~~	~~-11.9 (-26.8, 3.0)~~

~~**TABLE 16**~~
~~**Oropharyngeal Candidiasis Relapse Rates at 14 and 28 Days Post-Therapy in Patients with Oropharyngeal and Esophageal Candidiasis at Baseline**~~

	~~CANCIDAS~~	~~Fluconazole~~	~~% Difference* (95% CI)~~
~~Day 14 post-treatment~~	~~17/40 (42.5%)~~	~~7/53 (13.2%)~~	~~29.3 (11.5, 47.1)~~
~~Day 28 post-treatment~~	~~23/39 (59.0%)~~	~~18/51 (35.3%)~~	~~23.7 (3.4, 43.9)~~

TABLE 16
Oropharyngeal Candidiasis Response Rates at 5 to 7 Days Post-Therapy and Relapse Rates at 14 and 28 Days Post-Therapy in Patients with Oropharyngeal and Esophageal Candidiasis at Baseline

	CANCIDAS	Fluconazole	% Difference* (95% CI)
Response Rate Day 5-7 post-treatment	40/56 (71.4%)	55/66 (83.3%)	-11.9 (-26.8, 3.0)
Relapse Rate Day 14 post-treatment	17/40 (42.5%)	7/53 (13.2%)	29.3 (11.5, 47.1)
Relapse Rate Day 28 post-treatment	23/39 (59.0%)	18/51 (35.3%)	23.7 (3.4, 43.9)

* Calculated as CANCIDAS – fluconazole

In **14.4 Invasive Aspergillosis**, the last paragraph is revised as follows:

~~There is a substantial evidence that~~ CANCIDAS is ~~well tolerated and~~ effective for the treatment of invasive aspergillosis in patients who are refractory to or intolerant of itraconazole, amphotericin B, and/or lipid formulations of amphotericin B. However, the efficacy of CANCIDAS for initial treatment of invasive aspergillosis has not been evaluated in ~~concurrently~~ comparator-controlled clinical studies~~, with other antifungal therapies~~.

The **16 HOW SUPPLIED /STORAGE AND HANDLING**/***Storage and Handling***/*Reconstituted Concentrate* is revised as follows:

Reconstituted CANCIDAS in the vial may be stored at ≤25°C (≤77°F) for one hour prior to the preparation of the patient infusion solution.

The **17 PATIENT COUNSELING INFORMATION** section is revised as follows:

Inform patients that there have been isolated reports of serious hepatic effects from CANCIDAS therapy. Physicians will assess the risk/benefit of continuing CANCIDAS therapy if abnormal liver function tests occur during treatment.

Inform patients that CANCIDAS can cause hypersensitivity reactions, including rash, facial swelling, pruritus, sensation of warmth, or bronchospasm.

~~**17.1 Instructions**~~
~~Patient should be instructed to inform the doctor or healthcare provider about any medical conditions, medications, and about any allergies.~~
~~Patients should be instructed to inform the doctor or healthcare provider of any severe or unusual side effects.~~

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text submitted on June 23, 2009.

The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert. Please submit revised content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html, which is identical in content to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

Submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

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Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Rd.
Beltsville, MD 20705-1266
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Christina H. Chi, Ph.D., Regulatory Health Project Manager, at (301) 796 - 1600.

Sincerely,
{See appended electronic signature page}
Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Package Insert

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

/s/

Renata Albrecht

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