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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CANCIDAS safely and effectively. See full prescribing information for CANCIDAS.

CANCIDAS (caspofungin acetate) For Injection (IV Infusion Only)
Initial U.S. Approval: 2001

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	XX/200X
Dosage and Administration,	
Recommended Dosing in Pediatric Patients (2.3)	XX/200X
Preparation of CANCIDAS for Infusion (2.6)	XX/200X
Special Considerations for Pediatric Patients >3 Months of Age (2.6)	XX/200X

----------INDICATIONS AND USAGE----------

CANCIDAS® is an echinocandin antifungal drug that is indicated in adults and pediatric patients (3 months and older) for:

- **Empirical therapy** for presumed fungal infections in febrile, neutropenic patients. (1.1)
- **Treatment of Candidemia and the following *Candida* infections**: intra-abdominal abscesses, peritonitis and pleural space infections. (1.2)
- **Treatment of Esophageal Candidiasis**. (1.3)
- **Treatment of Invasive Aspergillosis** in patients who are refractory to or intolerant of other therapies (i.e., amphotericin B, lipid formulations of amphotericin B, and/or itraconazole). (1.4)

---------- DOSAGE AND ADMINISTRATION----------

For All Patients (2.1):

- Administer by slow intravenous 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 daily for all indications except esophageal candidiasis.
- For esophageal candidiasis, use 50 mg 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 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 daily dose of CANCIDAS for adult patients on rifampin.
- Consider dose increase to 70 mg CANCIDAS 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 daily (maximum daily dose not to exceed 70 mg).

----------DOSAGE FORMS AND STRENGTHS----------

- CANCIDAS 50 mg is a white to off-white powder/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)

---------- CONTRAINDICATIONS ----------

- CANCIDAS is contraindicated in patients with hypersensitivity to any component of this product. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Concomitant use of CANCIDAS with cyclosporine should be limited to patients for whom the potential benefit outweighs the potential risk. Patients who develop abnormal liver function tests during concomitant therapy should be monitored and the risk/benefit of continuing therapy should be evaluated. (5.1)
- Abnormalities in liver function tests and isolated cases of clinically significant hepatic dysfunction, hepatitis, and hepatic failure have been reported. Patients who develop abnormal liver function tests during CANCIDAS therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing CANCIDAS therapy. (5.2)

----------ADVERSE REACTIONS----------

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

To report SUSPECTED ADVERSE REACTIONS, contact Merck & Co., Inc. at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy – No human data. Adverse effects in animals. Use if potential benefits of treatment outweigh potential fetal 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)
- Safety and efficacy of CANCIDAS in neonates and infants less than 3 months old has not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: XX/200X

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CANCIDAS[1] is indicated in adults and pediatric patients (3 months and older) for:

1.1 Empirical therapy for presumed fungal infections in febrile, neutropenic patients

1.2 Treatment of Candidemia and the following *Candida* infections: intra-abdominal abscesses, peritonitis and pleural space infections. CANCIDAS has not been studied in endocarditis, osteomyelitis, and meningitis due to *Candida*.

1.3 Treatment of Esophageal Candidiasis *[see Clinical Studies (14.3)]*

1.4 Treatment of Invasive Aspergillosis in patients who are refractory to or intolerant of other therapies (i.e., amphotericin B, lipid formulations of amphotericin B, and/or itraconazole). CANCIDAS has not been studied as initial therapy for invasive aspergillosis.

2 DOSAGE AND ADMINISTRATION

2.1 Instructions for Use in All Patients

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

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.

2.2 Recommended Dosing in Adult Patients [≥18 years of age]

Empirical Therapy

A single 70-mg loading dose should be administered on Day 1, followed by 50 mg 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 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 should be 50 mg daily. 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 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

[1] Registered trademark of MERCK & CO., Inc.

increase in dose to 70 mg daily is well tolerated. The safety and efficacy of doses above 70 mg have not been adequately studied.

2.3 Recommended Dosing in Pediatric Patients [3 months to 17 years of age]

For all indications, a single 70-mg/m^2 loading dose should be administered on Day 1, followed by 50 mg/m^2 daily thereafter. **The maximum loading dose and the daily maintenance dose should not exceed 70 mg, regardless of the patient's calculated dose.** Dosing in pediatric patients (3 months to 17 years of age) should be based on the patient's Body Surface Area (BSA) as calculated by the following formula (Mosteller Formula *[see References (15)]*):

$$\text{BSA } (m^2) = \sqrt{\frac{\text{Height (cm)} \times \text{Weight (kg)}}{3600}}$$

Following calculation of the patient's BSA, the loading dose in milligrams should be calculated as BSA (m^2) X 70 mg/m^2. The maintenance dose in milligrams should be calculated as BSA (m^2) X 50 mg/m^2.

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). Although 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.

2.4 Patients with Hepatic Insufficiency

Adult patients with mild hepatic insufficiency (Child-Pugh score 5 to 6) do not need a dosage adjustment. For adult patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), CANCIDAS 35 mg 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 insufficiency (Child-Pugh score >9) and in pediatric patients with any degree of hepatic insufficiency.

2.5 Patients Receiving Concomitant Inducers of Drug Clearance

Adult patients on rifampin should receive 70 mg of CANCIDAS daily. Adult patients on nevirapine, efavirenz, carbamazepine, dexamethasone, or phenytoin may require an increase in dose to 70 mg of CANCIDAS 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 daily (not to exceed 70 mg) should be considered *[see Drug Interactions (7)].*

2.6 Preparation and Reconstitution for Administration

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.

Preparation of CANCIDAS for Infusion

1. Equilibrate the refrigerated vial of CANCIDAS to room temperature.
2. Aseptically add 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 to the vial.

Note: Each vial of CANCIDAS contains an intentional overfill of CANCIDAS. Thus, the drug concentration of the resulting solution is listed in Table 1 below.

TABLE 1
Information for Preparation of CANCIDAS

CANCIDAS vial	Total Drug Content	Reconstitution Volume	Resulting Concentration

	(including overfill)	to be added	following Reconstitution
50 mg	54.6 mg	10.8 mL	5 mg/mL
70 mg	75.6 mg	10.8 mL	7 mg/mL

The white to off-white cake will dissolve completely. Mix gently until a clear solution is obtained. Visually inspect the reconstituted solution for particulate matter or discoloration during reconstitution and prior to infusion. Do not use if the solution is cloudy or has precipitated.

The reconstituted solution may be stored for up to one hour at ≤25°C (≤77°F).

CANCIDAS vials are for single use only; the remaining solution should be discarded.

3. Aseptically transfer the appropriate volume (mL) of reconstituted CANCIDAS to an IV bag (or bottle) containing 250 mL of 0.9%, 0.45%, or 0.225% Sodium Chloride Injection or Lactated Ringers Injection. Alternatively, the volume (mL) of reconstituted CANCIDAS can be added to a reduced volume of 0.9%, 0.45%, or 0.225% Sodium Chloride Injection or Lactated Ringers Injection, not to exceed a final concentration of 0.5 mg/mL.

This infusion solution must be used within 24 hours if stored at ≤25°C (≤77°F) or within 48 hours if stored refrigerated at 2 to 8°C (36 to 46°F).

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. From the reconstituted solution in the vial, remove the volume of drug equal to the calculated loading dose or calculated maintenance dose based on a concentration of 7 mg/mL (if reconstituted from the 70-mg vial) or a concentration of 5 mg/mL (if reconstituted from the 50-mg vial).

The choice of vial should be based on total milligram dose of drug to be administered to the pediatric patient. To help ensure accurate dosing, it is recommended for pediatric doses less than 50 mg that 50-mg vials (with a concentration of 5 mg/mL) be used if available. The 70-mg vial should be reserved for pediatric patients requiring doses greater than 50 mg.

The maximum loading dose and the daily maintenance dose should not exceed 70 mg, regardless of the patient's calculated dose.

3 DOSAGE FORMS AND STRENGTHS

CANCIDAS 50 mg is a white to off-white powder/cake for infusion in a vial with a red aluminum band and a plastic cap. CANCIDAS 50-mg vial contains 54.6 mg of caspofungin.

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. CANCIDAS 70-mg vial contains 75.6 mg of caspofungin.

4 CONTRAINDICATIONS

CANCIDAS is contraindicated in patients with hypersensitivity to any component of this product.

5 WARNINGS AND PRECAUTIONS

5.1 Concomitant Use with Cyclosporine

Concomitant use of CANCIDAS with cyclosporine should be limited to patients for whom the potential benefit outweighs the potential risk. In one clinical study, 3 of 4 healthy adult subjects who received CANCIDAS 70 mg 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 alanine transaminase (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 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 both groups, elevations in aspartate transaminase (AST) paralleled ALT elevations, but were of lesser magnitude *[see Adverse Reactions, Concomitant Therapy (6.1)].*

In a retrospective 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). Fourteen patients (35%) developed transaminase elevations >5X upper limit of normal or >3X baseline during concomitant therapy or the 14-day follow-up period; five were considered possibly related to concomitant therapy. One patient had elevated bilirubin considered possibly related to concomitant therapy. No patient developed clinical evidence of hepatotoxicity or serious hepatic events. Discontinuations due to laboratory abnormalities in hepatic enzymes from any cause occurred in four patients. Of these, 2 were considered possibly related to therapy with CANCIDAS and/or cyclosporine as well as to other possible causes.

In the prospective invasive aspergillosis and compassionate use studies, there were 4 adult patients treated with CANCIDAS (50 mg/day) and cyclosporine for 2 to 56 days. None of these patients experienced increases in hepatic enzymes.

Given the limitations of these data, CANCIDAS and cyclosporine should only be used concomitantly in those patients for whom the potential benefit outweighs the potential risk. Patients who develop abnormal liver function tests during concomitant therapy should be monitored and the risk/benefit of continuing therapy should be evaluated.

5.2 Hepatic Effects

Laboratory abnormalities in liver function tests have been seen in healthy volunteers and patients treated with CANCIDAS. In some patients with serious underlying conditions who were receiving multiple concomitant medications with CANCIDAS, isolated cases of clinically significant hepatic dysfunction, hepatitis, and hepatic failure have been reported; a causal relationship to CANCIDAS has not been established. Patients who develop abnormal liver function tests during CANCIDAS therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing CANCIDAS therapy.

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).

6 ADVERSE REACTIONS

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.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of CANCIDAS cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does provide a basis for identifying adverse reactions that appear to be related to drug use and for approximating rates.

6.1 Clinical Trials Experience in Adults

The overall safety of caspofungin was assessed in 1661 adult individuals who received single or multiple doses of caspofungin acetate: 564 febrile, neutropenic patients (empirical therapy study); 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 the empirical therapy study patients had undergone hematopoietic stem-cell transplantation or chemotherapy. In the studies involving patients with documented *Candida* infections, the majority of the patients had serious underlying medical conditions (e.g., hematologic or other malignancy, recent major surgery, HIV) requiring multiple concomitant medications. Patients in the noncomparative *Aspergillus* studies often had serious predisposing medical conditions (e.g., bone marrow or peripheral stem cell

transplants, hematologic malignancy, solid tumors or organ transplants) requiring multiple concomitant medications.

Empirical Therapy

In the randomized, double-blinded empirical therapy study, patients received either CANCIDAS 50 mg/day (following a 70-mg loading dose) or AmBisome®[2] (amphotericin B liposome for injection, 3.0 mg/kg/day). In this study clinical or laboratory hepatic adverse reactions were reported in 39% and 45% of patients in the CANCIDAS and AmBisome groups, respectively. Also reported was an isolated, serious adverse reaction of hyperbilirubinemia considered possibly related to CANCIDAS. Adverse reactions occurring in ≥7.5% of the patients in either treatment group are presented in Table 2.

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

Within any system organ class, individuals may experience more than 1 adverse reaction.
* Regardless of causality
† 70 mg on Day 1, then 50 mg 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.

[2] Registered trademark of Gilead Sciences, Inc.

The proportion of patients who experienced an infusion-related adverse reaction[3] was significantly lower in the group treated with CANCIDAS (35.1%) than in the group treated with AmBisome (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 (2.6%) than in the group treated with AmBisome (11.5%). Clinical renal events, regardless of causality, were similar between CANCIDAS (75/564, 13.3%) and AmBisome (85/547, 15.5%).

Candidemia and Other Candida Infections [see Clinical Studies (14.2)]

In the randomized, double-blinded invasive candidiasis study, patients received either CANCIDAS 50 mg/day (following a 70-mg loading dose) or amphotericin B 0.6 to 1.0 mg/kg/day. Adverse reactions occurring in ≥10% of the patients in either treatment group are presented in Table 3.

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	**95.6**	**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

Within any system organ class, individuals may experience more than 1 adverse reaction.

* Intra-abdominal abscesses, peritonitis and pleural space infections.

† Regardless of causality

[3] 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.

‡Patients received CANCIDAS 70 mg on Day 1, then 50 mg daily for the remainder of their treatment.

The proportion of patients who experienced an infusion-related adverse reaction[4] was significantly lower in the group treated with CANCIDAS (20.2%) than in the group treated with amphotericin B (48.8%).

To evaluate the effect of CANCIDAS and amphotericin B 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. In a subgroup of patients whose baseline creatinine clearance was >30 mL/min, the incidence of nephrotoxicity was significantly lower in the group treated with CANCIDAS than in the group treated with amphotericin B.

Esophageal Candidiasis and Oropharyngeal Candidiasis

Adverse reactions occurring in ≥10% of patients with esophageal and/or oropharyngeal candidiasis are presented in Table 4.

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

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.

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 (21.7%), hypotension (20.3%), respiratory failure (20.3%), pyrexia (17.4%), diarrhea (14.5%), nausea (14.5%), headache (14.5%), 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, 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

[4] 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.

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)]*.

6.2 Clinical Trials Experience in Pediatric Patients (3 months to 17 years of age)

The overall safety of caspofungin was assessed in 171 pediatric patients who received single or multiple doses of CANCIDAS. The distribution among the 153 pediatric patients who were over the age of 3 months was as follows: 104 febrile, neutropenic patients; 38 patients with candidemia and/or intra-abdominal abscesses, peritonitis, or pleural space infections; 1 patient with esophageal candidiasis; and 10 patients with invasive aspergillosis. The overall safety profile of CANCIDAS in pediatric patients is comparable to that in adult patients. Table 5 shows the incidence of adverse reactions reported in ≥7.5% of pediatric patients in clinical studies.

One patient (0.6%) receiving CANCIDAS, and three patients (11.5%) receiving AmBisome developed a serious drug-related adverse reaction. Two patients (1.2%) were discontinued from CANCIDAS and three patients (11.5%) were discontinued from AmBisome due to a drug-related adverse reaction. The proportion of patients who experienced an infusion-related adverse reaction[5] was 21.6% in the group treated with CANCIDAS and 34.6% in the group treated with AmBisome.

TABLE 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	Comparator-Controlled Clinical Study of Empirical Therapy	
	CANCIDAS Any Dose N=115 (percent)	CANCIDAS 50 mg/m^2† N=56 (percent)	AmBisome 3 mg/kg N=26 (percent)
All Systems, Any Adverse Reaction	**94.8**	**96.4**	**88.5**
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

[5] 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.

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

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 daily for the remainder of the treatment.

6.3 Overall Safety Experience of CANCIDAS in Clinical Trials

The overall safety of CANCIDAS was assessed in 1832 individuals (including 1438 adult or pediatric patients and 394 volunteers) from 33 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 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.

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

TABLE 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 = 1747)	
	n	(%)
All Systems, Any Adverse Reaction	**1496**	**(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)

* 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, are listed below.

- ***Blood and lymphatic system disorders:*** anemia, coagulopathy, febrile neutropenia, neutropenia, thrombocytopenia
- ***Cardiac disorders:*** arrhythmia, atrial fibrillation, bradycardia, cardiac arrest, myocardial infarction, tachycardia
- ***Gastrointestinal disorders:*** abdominal distension, abdominal pain upper, constipation, dyspepsia
- ***General disorders and administration site conditions:*** asthenia, fatigue, infusion site pain/pruritus/swelling, mucosal inflammation, edema
- ***Hepatobiliary disorders:*** hepatic failure, hepatomegaly, hepatotoxicity, hyperbilirubinemia, jaundice
- ***Infections and infestations:*** bacteremia, sepsis, urinary tract infection
- ***Metabolic and nutrition disorders:*** anorexia, decreased appetite, fluid overload, hypomagnesemia, hypercalcemia, hyperglycemia, hypokalemia
- ***Musculoskeletal, connective tissue, and bone disorders:*** arthralgia, back pain, pain in extremity
- ***Nervous system disorders:*** convulsion, dizziness, somnolence, tremor
- ***Psychiatric disorders:*** anxiety, confusional state, depression, insomnia
- ***Renal and urinary disorders:*** hematuria, renal failure
- ***Respiratory, thoracic, and mediastinal disorders:*** dyspnea, epistaxis, hypoxia, tachypnea
- ***Skin and subcutaneous tissue disorders:*** erythema, petechiae, skin lesion, urticaria
- ***Vascular disorders:*** flushing, hypertension, phlebitis

6.4 Postmarketing Experience

The following additional adverse reactions have been identified during the post-approval use of caspofungin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Gastrointestinal disorders:* pancreatitis
- *Hepatobiliary disorders:* hepatic necrosis
- *Skin and subcutaneous tissue disorders*: erythema multiforme, Stevens-Johnson, skin exfoliation
- *Renal and urinary disorders:* clinically significant renal dysfunction
- *General disorders and administration site conditions:* swelling and peripheral edema

7 DRUG INTERACTIONS

[See Clinical Pharmacology (12.3).]

In clinical studies, caspofungin did not induce the CYP3A4 metabolism of other drugs. Caspofungin is not a substrate for P-glycoprotein and is a poor substrate for cytochrome P450 enzymes.

Clinical studies in adult healthy volunteers show that the pharmacokinetics of CANCIDAS are not altered by itraconazole, amphotericin B, mycophenolate, nelfinavir, or tacrolimus. CANCIDAS has no effect on the pharmacokinetics of itraconazole, amphotericin B, or the active metabolite of mycophenolate.

Tacrolimus: For patients receiving CANCIDAS and tacrolimus, standard monitoring of tacrolimus blood concentrations and appropriate tacrolimus dosage adjustments are recommended.

Cyclosporine: In two adult clinical studies, cyclosporine (one 4-mg/kg dose or two 3-mg/kg doses) increased the AUC of caspofungin by approximately 35%. CANCIDAS did not increase the plasma levels of cyclosporine. There were transient increases in liver ALT and AST when CANCIDAS and cyclosporine were co-administered *[see Warnings and Precautions (5.1) and Adverse Reactions, Concomitant Therapy (6.1)].*

Rifampin: Adult patients on rifampin should receive 70 mg of CANCIDAS daily.

Other inducers of drug clearance:

Adults: When CANCIDAS is co-administered to adult patients with inducers of drug clearance, such as efavirenz, nevirapine, phenytoin, dexamethasone, or carbamazepine, use of a daily dose of 70 mg of CANCIDAS should be considered.

Pediatric Patients: 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 daily (not to exceed an actual daily dose of 70 mg) should be considered.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies with the use of CANCIDAS in pregnant women. In animal studies, caspofungin caused embryofetal toxicity, including increased resorptions, increased peri-implantation loss, and incomplete ossification at multiple fetal sites. CANCIDAS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In offspring born to pregnant rats treated with caspofungin at doses comparable to the human dose based on body surface area comparisons, there was incomplete ossification of the skull and torso and increased incidences of cervical rib. There was also an increase in resorptions and peri-implantation losses. In pregnant rabbits treated with caspofungin at doses comparable to 2 times the human dose based on body surface area comparisons, there was an increased incidence of incomplete ossification of the talus/calcaneus in offspring and increases in fetal resorptions. Caspofungin crossed the placenta in rats and rabbits and was detectable in fetal plasma.

8.3 Nursing Mothers

It is not known whether caspofungin is present in human milk. Caspofungin was found in the milk of lactating, drug-treated rats. Because many drugs are excreted in human milk, caution should be exercised when caspofungin is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of CANCIDAS in pediatric patients 3 months to 17 years of age are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in pediatric patients, and additional data from prospective studies in pediatric patients 3 months to 17 years of age for the following indications *[see Indications and Usage (1)]:*

- Empirical therapy for presumed fungal infections in febrile, neutropenic patients.
- Treatment of candidemia and the following *Candida* infections: intra-abdominal abscesses, peritonitis, and pleural space infections.
- Treatment of esophageal candidiasis.
- Treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies (i.e., amphotericin B, lipid formulations of amphotericin B, and/or itraconazole).

The efficacy and safety of CANCIDAS has not been adequately studied in prospective clinical trials involving neonates and infants under 3 months of age. Although limited pharmacokinetic data were collected in neonates and infants below 3 months of age, these data are insufficient to establish a safe and effective dose of caspofungin in the treatment of neonatal candidiasis. Invasive candidiasis in neonates has a higher rate of CNS and multi-organ involvement than in older patients; the ability of CANCIDAS to penetrate the blood-brain barrier and to treat patients with meningitis and endocarditis is unknown.

CANCIDAS has not been studied in pediatric patients with endocarditis, osteomyelitis, and meningitis due to *Candida*. CANCIDAS has also not been studied as initial therapy for invasive aspergillosis in pediatric patients.

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 (11.7%), rash (11.7%), increased alanine aminotransferase (11.1%), hypotension (11.1%), and chills (11.1%). *[See Adverse Reactions (6.2).]*

8.5 Geriatric Use

Clinical studies of CANCIDAS did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Although the number of elderly

patients was not large enough for a statistical analysis, no overall differences in safety or efficacy were observed between these and younger patients. Plasma concentrations of caspofungin in healthy older men and women (≥65 years of age) were increased slightly (approximately 28% in AUC) compared to young healthy men. A similar effect of age on pharmacokinetics was seen in patients with candidemia or other *Candida* infections (intra-abdominal abscesses, peritonitis, or pleural space infections). No dose adjustment is recommended for the elderly; however, greater sensitivity of some older individuals cannot be ruled out.

8.6 Patients with Hepatic Insufficiency

Adult patients with mild hepatic insufficiency (Child-Pugh score 5 to 6) do not need a dosage adjustment. For adult patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), CANCIDAS 35 mg 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 insufficiency (Child-Pugh score >9) and in pediatric patients 3 months to 17 years of age with any degree of hepatic insufficiency.

8.7 Patients with Renal Insufficiency

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

10 OVERDOSAGE

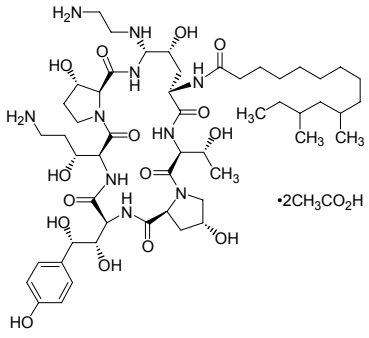
In adult clinical studies the highest dose was 210 mg, administered as a single dose to 6 healthy subjects. This dose was generally well tolerated. In addition, 100 mg once daily for 21 days has been administered to 15 healthy subjects and was generally well tolerated. Caspofungin is not dialyzable. 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) 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.

11 DESCRIPTION

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 (echinocandins) that inhibit the synthesis of β (1,3)-D-glucan, an integral component of the fungal cell wall.

CANCIDAS (caspofungin acetate) is 1-[(4*R*,5*S*)-5-[(2-aminoethyl)amino]-N^2-(10,12-dimethyl-1-oxotetradecyl)-4-hydroxy-L-ornithine]-5-[(3*R*)-3-hydroxy-L-ornithine] pneumocandin B_0 diacetate (salt). CANCIDAS 50 mg also contains: 39 mg sucrose, 26 mg mannitol, glacial acetic acid, and sodium hydroxide. CANCIDAS 70 mg also contains 54 mg sucrose, 36 mg mannitol, glacial acetic acid, and sodium hydroxide. Caspofungin acetate is a hygroscopic, white to off-white powder. It is freely soluble in water and methanol, and slightly soluble in ethanol. The pH of a saturated aqueous solution of caspofungin acetate is approximately 6.6. The empirical formula is $C_{52}H_{88}N_{10}O_{15}$•$2C_2H_4O_2$ and the formula weight is 1213.42. The structural formula is:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

Distribution

Plasma concentrations of caspofungin decline in a polyphasic manner following single 1-hour IV infusions. A short α-phase occurs immediately postinfusion, followed by a β-phase (half-life of 9 to 11 hours) that characterizes much of the profile and exhibits clear log-linear behavior from 6 to 48 hours postdose during which the plasma concentration decreases 10-fold. An additional, longer half-life phase, γ-phase, (half-life of 40-50 hours), also occurs. Distribution, rather than excretion or biotransformation, is the dominant mechanism influencing plasma clearance. Caspofungin is extensively bound to albumin (~97%), and distribution into red blood cells is minimal. Mass balance results showed that approximately 92% of the administered radioactivity was distributed to tissues by 36 to 48 hours after a single 70-mg dose of [^{3}H] caspofungin acetate. There is little excretion or biotransformation of caspofungin during the first 30 hours after administration.

Metabolism

Caspofungin is slowly metabolized by hydrolysis and N-acetylation. Caspofungin also undergoes spontaneous chemical degradation to an open-ring peptide compound, L-747969. At later time points ($\geq$5 days postdose), there is a low level ($\leq$7 picomoles/mg protein, or $\leq$1.3% of administered dose) of covalent binding of radiolabel in plasma following single-dose administration of [^{3}H] caspofungin acetate, which may be due to two reactive intermediates formed during the chemical degradation of caspofungin to L-747969. Additional metabolism involves hydrolysis into constitutive amino acids and their degradates, including dihydroxyhomotyrosine and N-acetyl-dihydroxyhomotyrosine. These two tyrosine derivatives are found only in urine, suggesting rapid clearance of these derivatives by the kidneys.

Excretion

Two single-dose radiolabeled pharmacokinetic studies were conducted. In one study, plasma, urine, and feces were collected over 27 days, and in the second study plasma was collected over 6 months. Plasma concentrations of radioactivity and of caspofungin were similar during the first 24 to 48 hours postdose; thereafter drug levels fell more rapidly. In plasma, caspofungin concentrations fell below the limit of quantitation after 6 to 8 days postdose, while radiolabel fell below the limit of quantitation at 22.3 weeks postdose. After single intravenous administration of [^{3}H] caspofungin acetate, excretion of caspofungin and its metabolites in humans was 35% of dose in feces and 41% of dose in urine. A small amount of caspofungin is excreted unchanged in urine (~1.4% of dose). Renal clearance of parent drug is low (~0.15 mL/min) and total clearance of caspofungin is 12 mL/min.

Special Populations

Renal Insufficiency

In a clinical study of single 70-mg doses, caspofungin pharmacokinetics were similar in healthy adult volunteers with mild renal insufficiency (creatinine clearance 50 to 80 mL/min) and control subjects. Moderate (creatinine clearance 31 to 49 mL/min), advanced (creatinine clearance 5 to 30 mL/min), and end-stage (creatinine clearance <10 mL/min and dialysis dependent) renal 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 insufficiency. Caspofungin is not dialyzable, thus supplementary dosing is not required following hemodialysis.

Hepatic Insufficiency

Plasma concentrations of caspofungin after a single 70-mg dose in adult patients with mild hepatic 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 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 insufficiency. Adult patients with moderate hepatic 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 insufficiency based upon this pharmacokinetic data *[see Dosage and Administration (2.4)]*. There is no clinical experience in adult patients with severe hepatic insufficiency (Child-Pugh score >9) or in pediatric patients with any degree of hepatic insufficiency.

Gender

Plasma concentrations of caspofungin in healthy adult men and women were similar following a single 70-mg dose. After 13 daily 50-mg doses, caspofungin plasma concentrations in women were elevated slightly (approximately 22% in area under the curve [AUC]) relative to men. No dosage adjustment is necessary based on gender.

Geriatric

Plasma concentrations of caspofungin in healthy older men and women (≥65 years of age) were increased slightly (approximately 28% AUC) compared to young healthy men after a single 70-mg dose of caspofungin. In patients who were treated empirically or who had candidemia or other *Candida* infections (intra-abdominal abscesses, peritonitis, or pleural space infections), a similar modest effect of age was seen in older patients relative to younger patients. No dosage adjustment is necessary for the elderly *[see Use in Specific Populations (8.5)].*

Pediatric

CANCIDAS has been studied in five prospective studies involving pediatric patients under 18 years of age, including three pediatric pharmacokinetic studies [initial study in adolescents (12-17 years of age) and children (2-11 years of age) followed by a study in younger patients (3-23 months of age) and then followed by a study in neonates and infants (<3 months)] *[see Use in Specific Populations(8.4)]*.

Pharmacokinetic parameters following multiple doses of CANCIDAS in pediatric and adult patients are presented in Table 7.

TABLE 7
Pharmacokinetic Parameters Following Multiple Doses of CANCIDAS in Pediatric (3 months to 17 years) and Adult Patients

Population	N	Daily Dose	Pharmacokinetic Parameters (Mean ± Standard Deviation)				
			$AUC_{0\text{-}24hr}$ (µg·hr/mL)	C_{1hr} (µg/mL)	C_{24hr} (µg/mL)	$t_{1/2}$ (hr)*	Cl (mL/min)
PEDIATRIC PATIENTS							
Adolescents, Aged 12-17 years	8	50 mg/m^2	124.9 ± 50.4	14.0 ± 6.9	2.4 ± 1.0	11.2 ± 1.7	12.6 ± 5.5
Children, Aged 2-11 years	9	50 mg/m^2	120.0 ± 33.4	16.1 ± 4.2	1.7 ± 0.8	8.2 ± 2.4	6.4 ± 2.6
Young Children, Aged 3-23 months	8	50 mg/m^2	131.2 ± 17.7	17.6 ± 3.9	1.7 ± 0.7	8.8 ± 2.1	3.2 ± 0.4
ADULT PATIENTS							
Adults with Esophageal Candidiasis	6†	50 mg	87.3 ± 30.0	8.7 ± 2.1	1.7 ± 0.7	13.0 ± 1.9	10.6 ± 3.8
Adults receiving Empirical Therapy	119‡	50 mg§	--	8.0 ± 3.4	1.6 ± 0.7	--	--

* Harmonic Mean ± jackknife standard deviation
† N=5 for C_{1hr} and $AUC_{0\text{-}24hr}$; N=6 for C_{24hr}
‡ N=117 for C_{24hr}; N=119 for C_{1hr}
§ Following an initial 70-mg loading dose on day 1

Race

Regression analyses of patient pharmacokinetic data indicated that no clinically significant differences in the pharmacokinetics of caspofungin were seen among Caucasians, Blacks, and Hispanics. No dosage adjustment is necessary on the basis of race.

Drug Interactions [see Drug Interactions (7)]

Studies *in vitro* show that caspofungin acetate is not an inhibitor of any enzyme in the cytochrome P450 (CYP) system. In clinical studies, caspofungin did not induce the CYP3A4 metabolism of other drugs. Caspofungin is not a substrate for P-glycoprotein and is a poor substrate for cytochrome P450 enzymes.

Clinical studies in adult healthy volunteers show that the pharmacokinetics of CANCIDAS are not altered by itraconazole, amphotericin B, mycophenolate, nelfinavir, or tacrolimus. CANCIDAS has no effect on the pharmacokinetics of itraconazole, amphotericin B, or the active metabolite of mycophenolate.

Tacrolimus: CANCIDAS reduced the blood AUC_{0-12} of tacrolimus (FK-506, Prograf®[6]) by approximately 20%, peak blood concentration (C_{max}) by 16%, and 12-hour blood concentration (C_{12hr}) by 26% in healthy adult subjects when tacrolimus (2 doses of 0.1 mg/kg 12 hours apart) was administered on the 10th day of CANCIDAS 70 mg daily, as compared to results from a control period in which tacrolimus was administered alone. For patients receiving both therapies, standard monitoring of tacrolimus blood concentrations and appropriate tacrolimus dosage adjustments are recommended.

Cyclosporine: In two adult clinical studies, cyclosporine (one 4 mg/kg dose or two 3 mg/kg doses) increased the AUC of caspofungin by approximately 35%. CANCIDAS did not increase the plasma levels of cyclosporine. There were transient increases in liver ALT and AST when CANCIDAS and cyclosporine were co-administered *[see Warnings and Precautions (5.1) and Adverse Reactions, Concomitant Therapy (6.1)].*

Rifampin: A drug-drug interaction study with rifampin in adult healthy volunteers has shown a 30% decrease in caspofungin trough concentrations. Adult patients on rifampin should receive 70 mg of CANCIDAS daily.

Other inducers of drug clearance

Adults: In addition, results from regression analyses of adult patient pharmacokinetic data suggest that co-administration of other inducers of drug clearance (efavirenz, nevirapine, phenytoin, dexamethasone, or carbamazepine) with CANCIDAS may result in clinically meaningful reductions in caspofungin concentrations. It is not known which drug clearance mechanism involved in caspofungin disposition may be inducible. When CANCIDAS is co-administered to adult patients with inducers of drug clearance, such as efavirenz, nevirapine, phenytoin, dexamethasone, or carbamazepine, use of a daily dose of 70 mg of CANCIDAS should be considered.

Pediatric patients: In pediatric patients, results from regression analyses of pharmacokinetic data suggest that co-administration of dexamethasone with CANCIDAS may result in clinically meaningful reductions in caspofungin trough concentrations. This finding may indicate that pediatric patients will have similar reductions with inducers as seen in adults. 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 daily (not to exceed an actual daily dose of 70 mg) should be considered.

12.4 Microbiology

Mechanism of Action

Caspofungin acetate, the active ingredient of CANCIDAS, 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. Caspofungin has shown activity against *Candida* species and in regions of active cell growth of the hyphae of *Aspergillus fumigatus*.

Activity in vitro

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
Candida tropicalis

Susceptibility Testing Methods [see References (15)]

Aspergillus Species and Other Filamentous fungi

No interpretive criteria have been established for *Aspergillus* species and other filamentous fungi.

[6] Registered trademark of Astellas Pharma, Inc.

Candida Species

The interpretive standards for caspofungin against *Candida* species are applicable only to tests performed using Clinical Laboratory and Standards Institute (CLSI) microbroth dilution reference method M27A for MIC (partial inhibition endpoint) read at 24 hours.

Broth Microdilution Techniques: Quantitative methods are used to determine antifungal minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of *Candida* spp. to antifungal agents. MICs should be determined using a standardized procedure at 24 hours *[see References (15)]*. Standardized procedures are based on a microdilution method (broth) with standardized inoculum concentrations and standardized concentrations of caspofungin powder. The MIC values should be interpreted according to the criteria provided in Table 8.

TABLE 8
Susceptibility Interpretive Criteria for Caspofungin

Pathogen	Broth Microdilution MIC* (µg/mL) at 24 hours		
	S	I	R
Candida species	≤2	(†)	(†)

* A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable.

† The current absence of data on caspofungin-resistant isolates precludes defining any categories other than "Susceptible." Isolates yielding test results suggestive of a "Non-Susceptible" category should be retested, and if the result is confirmed, the isolate should be submitted to a reference laboratory for further testing.

Quality Control

Standardized susceptibility test procedures require the use of quality control organisms to control the technical aspects of the test procedures. Standard caspofungin powder should provide the following range of values noted in Table 9.

NOTE: Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within fungi; the specific strains used for microbiological control are not clinically significant.

TABLE 9
Acceptable Quality Control Ranges* for Caspofungin to be used in Validation of Susceptibility Test Results

QC strain	Broth microdilution (MIC in µg/mL) at 24-hour
Candida parapsilosis ATCC† 22019	0.25 – 1.0
Candida krusei ATCC 6258	0.12 – 1.0

* Quality control ranges have not been established for this strain/antifungal agent combination due to their extensive interlaboratory variation during initial quality control studies.

† ATCC is a registered trademark of the American Type Culture Collection.

Activity in vivo

Caspofungin was active when parenterally administered to immunocompetent and immunosuppressed mice as long as 24 hours after disseminated infections with *C. albicans,* in which the endpoints were prolonged survival of infected mice and reduction of *C. albicans* from target organs. Caspofungin, administered parenterally to immunocompetent and immunosuppressed rodents, as long as 24 hours after disseminated or pulmonary infection with *Aspergillus fumigatus*, has shown prolonged survival, which has not been consistently associated with a reduction in mycological burden.

Drug Resistance

A caspofungin MIC of ≤2 µg/mL (Susceptible) indicates that the *Candida* isolate is likely to be inhibited if caspofungin therapeutic concentrations are achieved; there is insufficient treatment outcome information on isolates with reduced caspofungin susceptibility to define categories other than susceptible. Breakthrough infections with *Candida* isolates requiring caspofungin concentrations >2 µg/mL for growth inhibition have developed in a mouse model of *C. albicans* infection and in some patients with *Candida* infections. Some of these isolates had mutations in the FKS1 gene. The incidence of drug resistance by various clinical isolates of *Candida* and *Aspergillus* species is unknown.

Drug Interactions

Studies *in vitro* and *in vivo* of caspofungin, in combination with amphotericin B, suggest no antagonism of antifungal activity against either *A. fumigatus* or *C. albicans*. The clinical significance of these results is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate the carcinogenic potential of caspofungin.

Caspofungin did not show evidence of mutagenic or genotoxic potential when evaluated in the following *in vitro* assays: bacterial (Ames) and mammalian cell (V79 Chinese hamster lung fibroblasts) mutagenesis assays, the alkaline elution/rat hepatocyte DNA strand break test, and the chromosome aberration assay in Chinese hamster ovary cells. Caspofungin was not genotoxic when assessed in the mouse bone marrow chromosomal test at doses up to 12.5 mg/kg (equivalent to a human dose of 1 mg/kg based on body surface area comparisons), administered intravenously.

Fertility and reproductive performance were not affected by the intravenous administration of caspofungin to rats at doses up to 5 mg/kg. At 5 mg/kg exposures were similar to those seen in patients treated with the 70-mg dose.

13.2 Animal Toxicology and/or Pharmacology

In one 5-week study in monkeys at doses which produced exposures approximately 4 to 6 times those seen in adult patients treated with a 70-mg dose, scattered small foci of subcapsular necrosis were observed microscopically in the livers of some animals (2/8 monkeys at 5 mg/kg and 4/8 monkeys at 8 mg/kg); however, this histopathological finding was not seen in another study of 27 weeks duration at similar doses.

No treatment-related findings were seen in a 5-week study in infant monkeys at doses which produced exposures approximately 3 times those achieved in pediatric patients receiving a maintenance dose of 50 mg/m^2 daily.

14 CLINICAL STUDIES

The results of the adult clinical studies are presented by indications in Section 14.1 to 14.4. Results of pediatric clinical trials are in Section 14.5.

14.1 Empirical Therapy in Febrile, Neutropenic Patients

A double-blind study enrolled 1111 febrile, neutropenic (<500 cells/mm^3) patients who were randomized to treatment with daily doses of CANCIDAS (50 mg/day following a 70-mg loading dose on Day 1) or AmBisome (3.0 mg/kg/day). Patients were stratified based on risk category (high-risk patients had undergone allogeneic stem cell transplantation or had relapsed acute leukemia) and on receipt of prior antifungal prophylaxis. Twenty-four percent of patients were high risk and 56% had received prior antifungal prophylaxis. Patients who remained febrile or clinically deteriorated following 5 days of therapy could receive 70 mg/day of CANCIDAS or 5.0 mg/kg/day of AmBisome. Treatment was continued to resolution of neutropenia (but not beyond 28 days unless a fungal infection was documented).

An overall favorable response required meeting each of the following criteria: no documented breakthrough fungal infections up to 7 days after completion of treatment, survival for 7 days after completion of study therapy, no discontinuation of the study drug because of drug-related toxicity or lack of efficacy, resolution of fever during the period of neutropenia, and successful treatment of any documented baseline fungal infection.

Based on the composite response rates, CANCIDAS was as effective as AmBisome in empirical therapy of persistent febrile neutropenia (see Table 10).

TABLE 10
Favorable Response of Patients with Persistent Fever and Neutropenia

	CANCIDAS*	AmBisome*	% Difference (Confidence Interval)†
Number of Patients‡	556	539	
Overall Favorable Response	190 (33.9%)	181 (33.7%)	0.2 (-5.6, 6.0)
No documented breakthrough fungal infection	527 (94.8%)	515 (95.5%)	-0.8
Survival 7 days after end of treatment	515 (92.6%)	481 (89.2%)	3.4

No discontinuation due to toxicity or lack of efficacy	499 (89.7%)	461 (85.5%)	4.2
Resolution of fever during neutropenia	229 (41.2%)	223 (41.4%)	-0.2

* CANCIDAS: 70 mg on Day 1, then 50 mg daily for the remainder of treatment (daily dose increased to 70 mg for 73 patients); AmBisome: 3.0 mg/kg/day (daily dose increased to 5.0 mg/kg for 74 patients).

† Overall Response: estimated % difference adjusted for strata and expressed as CANCIDAS – AmBisome (95.2% CI); Individual criteria presented above are not mutually exclusive. The percent difference calculated as CANCIDAS – AmBisome.

‡ Analysis population excluded subjects who did not have fever or neutropenia at study entry.

The rate of successful treatment of documented baseline infections, a component of the primary endpoint, was not statistically different between treatment groups.

The response rates did not differ between treatment groups based on either of the stratification variables: risk category or prior antifungal prophylaxis.

14.2 Candidemia and the following other *Candida* infections: intra-abdominal abscesses, peritonitis and pleural space infections

In a Phase III randomized, double-blind study, patients with a proven diagnosis of invasive candidiasis received daily doses of CANCIDAS (50 mg/day following a 70-mg loading dose on Day 1) or amphotericin B deoxycholate (0.6 to 0.7 mg/kg/day for non-neutropenic patients and 0.7 to 1.0 mg/kg/day for neutropenic patients). Patients were stratified by both neutropenic status and APACHE II score. Patients with *Candida* endocarditis, meningitis, or osteomyelitis were excluded from this study.

Patients who met the entry criteria and received one or more doses of IV study therapy were included in the modified intention-to-treat [MITT] analysis of response at the end of IV study therapy. A favorable response at this time point required both symptom/sign resolution/improvement and microbiological clearance of the *Candida* infection.

Two hundred thirty-nine patients were enrolled. Patient disposition is shown in Table 11.

TABLE 11
Disposition in Candidemia and Other *Candida* Infections
(Intra-abdominal abscesses, peritonitis, and pleural space infections)

	CANCIDAS*	Amphotericin B
Randomized patients	114	125
Patients completing study†	63 (55.3%)	69 (55.2%)
DISCONTINUATIONS OF STUDY†		
All Study Discontinuations	51 (44.7%)	56 (44.8%)
Study Discontinuations due to clinical adverse events	39 (34.2%)	43 (34.4%)
Study Discontinuations due to laboratory adverse events	0 (0%)	1 (0.8%)
DISCONTINUATIONS OF STUDY THERAPY		
All Study Therapy Discontinuations	48 (42.1%)	58 (46.4%)
Study Therapy Discontinuations due to clinical adverse events	30 (26.3%)	37 (29.6%)
Study Therapy Discontinuations due to laboratory adverse events	1 (0.9%)	7 (5.6%)
Study Therapy Discontinuations due to all drug-related‡ adverse events	3 (2.6%)	29 (23.2%)

* Patients received CANCIDAS 70 mg on Day 1, then 50 mg daily for the remainder of their treatment.

† Study defined as study treatment period and 6-8 week follow-up period.

‡ Determined by the investigator to be possibly, probably, or definitely drug-related.

Of the 239 patients enrolled, 224 met the criteria for inclusion in the MITT population (109 treated with CANCIDAS and 115 treated with amphotericin B). Of these 224 patients, 186 patients had candidemia (92 treated with CANCIDAS and 94 treated with amphotericin B). The majority of the patients with candidemia were non-neutropenic (87%) and had an APACHE II score less than or equal to 20 (77%) in both arms. Most candidemia infections were caused by *C. albicans* (39%), followed by *C. parapsilosis* (20%), *C. tropicalis* (17%), *C. glabrata* (8%), and *C. krusei* (3%).

At the end of IV study therapy, CANCIDAS was comparable to amphotericin B in the treatment of candidemia in the MITT population. For the other efficacy time points (Day 10 of IV study therapy, end of all antifungal therapy, 2-week post-therapy follow-up, and 6- to 8-week post-therapy follow-up), CANCIDAS was as effective as amphotericin B.

Outcome, relapse and mortality data are shown in Table 12.

TABLE 12
Outcomes, Relapse, & Mortality in Candidemia and Other *Candida* Infections (Intra-abdominal abscesses, peritonitis, and pleural space infections)

	CANCIDAS*	Amphotericin B	% Difference† after adjusting for strata (Confidence Interval)‡
Number of MITT§ patients	109	115	
FAVORABLE OUTCOMES (MITT) AT THE END OF IV STUDY THERAPY			

All MITT patients	81/109 (74.3%)	78/115 (67.8%)	7.5 (-5.4, 20.3)
Candidemia	67/92 (72.8%)	63/94 (67.0%)	7.0 (-7.0, 21.1)
Neutropenic	6/14 (43%)	5/10 (50%)	
Non-neutropenic	61/78 (78%)	58/84 (69%)	
Endophthalmitis	0/1	2/3	
Multiple Sites	4/5	4/4	
Blood / Pleural	1/1	1/1	
Blood / Peritoneal	1/1	1/1	
Blood / Urine	-	1/1	
Peritoneal / Pleural	1/2	-	
Abdominal / Peritoneal	-	1/1	
Subphrenic / Peritoneal	1/1	-	
DISSEMINATED INFECTIONS, RELAPSES AND MORTALITY			
Disseminated Infections in neutropenic patients	4/14 (28.6%)	3/10 (30.0%)	
All relapses¶	7/81 (8.6%)	8/78 (10.3%)	
Culture-confirmed relapse	5/81 (6%)	2/78 (3%)	
Overall study# mortality in MITT	36/109 (33.0%)	35/115 (30.4%)	
Mortality during study therapy	18/109 (17%)	13/115 (11%)	
Mortality attributed to *Candida*	4/109 (4%)	7/115 (6%)	

* Patients received CANCIDAS 70 mg on Day 1, then 50 mg daily for the remainder of their treatment.

† Calculated as CANCIDAS – amphotericin B

‡ 95% CI for candidemia, 95.6% for all patients

§ Modified intention-to-treat

¶ Includes all patients who either developed a culture-confirmed recurrence of *Candida* infection or required antifungal therapy for the treatment of a proven or suspected *Candida* infection in the follow-up period.

Study defined as study treatment period and 6-8 week follow-up period.

In this study, the efficacy of CANCIDAS in patients with intra-abdominal abscesses, peritonitis and pleural space *Candida* infections was evaluated in 19 non-neutropenic patients. Two of these patients had concurrent candidemia. *Candida* was part of a polymicrobial infection that required adjunctive surgical drainage in 11 of these 19 patients. A favorable response was seen in 9 of 9 patients with peritonitis, 3 of 4 with abscesses (liver, parasplenic, and urinary bladder abscesses), 2 of 2 with pleural space infections, 1 of 2 with mixed peritoneal and pleural infection, 1 of 1 with mixed abdominal abscess and peritonitis, and 0 of 1 with *Candida* pneumonia.

Overall, across all sites of infection included in the study, the efficacy of CANCIDAS was comparable to that of amphotericin B for the primary endpoint.

In this study, the efficacy data for CANCIDAS in neutropenic patients with candidemia were limited. In a separate compassionate use study, 4 patients with hepatosplenic candidiasis received prolonged therapy with CANCIDAS following other long-term antifungal therapy; three of these patients had a favorable response.

14.3 Esophageal Candidiasis (and information on oropharyngeal candidiasis)

The safety and efficacy of CANCIDAS in the treatment of esophageal candidiasis was evaluated in one large, controlled, noninferiority, clinical trial and two smaller dose-response studies.

In all 3 studies, patients were required to have symptoms and microbiological documentation of esophageal candidiasis; most patients had advanced AIDS (with CD4 counts <50/mm^3).

Of the 166 patients in the large study who had culture-confirmed esophageal candidiasis at baseline, 120 had *Candida albicans* and 2 had *Candida tropicalis* as the sole baseline pathogen whereas 44 had mixed baseline cultures containing *C. albicans* and one or more additional *Candida* species.

In the large, randomized, double-blind study comparing CANCIDAS 50 mg/day versus intravenous fluconazole 200 mg/day for the treatment of esophageal candidiasis, patients were treated for an average of 9 days (range 7-21 days). Favorable overall response at 5 to 7 days following discontinuation of study therapy required both complete resolution of symptoms and significant endoscopic improvement. The definition of endoscopic response was based on severity of disease at baseline using a 4-grade scale and required at least a two-grade reduction from baseline endoscopic score or reduction to grade 0 for patients with a baseline score of 2 or less.

The proportion of patients with a favorable overall response was comparable for CANCIDAS and fluconazole as shown in Table 13.

TABLE 13
Favorable Response Rates for Patients with Esophageal Candidiasis*

	CANCIDAS	Fluconazole	% Difference† (95% CI)
Day 5-7 post-treatment	66/81 (81.5%)	80/94 (85.1%)	-3.6 (-14.7, 7.5)

* Analysis excluded patients without documented esophageal candidiasis or patients not receiving at least 1 day of study therapy.

† Calculated as CANCIDAS – fluconazole

The proportion of patients with a favorable symptom response was also comparable (90.1% and 89.4% for CANCIDAS and fluconazole, respectively). In addition, the proportion of patients with a favorable endoscopic response was comparable (85.2% and 86.2% for CANCIDAS and fluconazole, respectively).

As shown in Table 14, the esophageal candidiasis relapse rates at the Day 14 post-treatment visit were similar for the two groups. At the Day 28 post-treatment visit, the group treated with CANCIDAS had a numerically higher incidence of relapse; however, the difference was not statistically significant.

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

	CANCIDAS	Fluconazole	% Difference* (95% CI)
Day 14 post-treatment	7/66 (10.6%)	6/76 (7.9%)	2.7 (-6.9, 12.3)
Day 28 post-treatment	18/64 (28.1%)	12/72 (16.7%)	11.5 (-2.5, 25.4)

* Calculated as CANCIDAS – fluconazole

In this trial, which was designed to establish noninferiority of CANCIDAS to fluconazole for the treatment of esophageal candidiasis, 122 (70%) patients also had oropharyngeal candidiasis. A favorable response was defined as complete resolution of all symptoms of oropharyngeal disease and all visible oropharyngeal lesions. The proportion of patients with a favorable oropharyngeal response at the 5- to 7-day post-treatment visit was numerically lower for CANCIDAS; however, the difference was not statistically significant. The results are shown in Table 15.

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)

* Calculated as CANCIDAS – fluconazole

As shown in Table 16, the oropharyngeal candidiasis relapse rates at the Day 14 and the Day 28 post-treatment visits were statistically significantly higher for CANCIDAS than for fluconazole.

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)

* Calculated as CANCIDAS – fluconazole

The results from the two smaller dose-ranging studies corroborate the efficacy of CANCIDAS for esophageal candidiasis that was demonstrated in the larger study.

CANCIDAS was associated with favorable outcomes in 7 of 10 esophageal *C. albicans* infections refractory to at least 200 mg of fluconazole given for 7 days, although the *in vitro* susceptibility of the infecting isolates to fluconazole was not known.

14.4 Invasive Aspergillosis

Sixty-nine patients between the ages of 18 and 80 with invasive aspergillosis (IA) were enrolled in an open-label, noncomparative study to evaluate the safety, tolerability, and efficacy of CANCIDAS. Enrolled patients had previously been refractory to or intolerant of other antifungal therapy(ies). Refractory patients were classified as those who had disease progression or failed to improve despite therapy for at least 7 days with amphotericin B, lipid formulations of amphotericin B, itraconazole, or an investigational azole with reported activity against *Aspergillus*. Intolerance to previous therapy was defined as a doubling of creatinine (or creatinine ≥2.5 mg/dL while on therapy), other acute reactions, or infusion-related toxicity. To be included in the study, patients with pulmonary disease must have had definite (positive tissue histopathology or positive culture from tissue obtained by an invasive procedure) or probable (positive radiographic or computed tomography evidence with supporting culture from bronchoalveolar lavage or sputum, galactomannan enzyme-linked immunosorbent assay, and/or polymerase chain reaction) invasive aspergillosis. Patients with extrapulmonary disease had to have definite invasive aspergillosis. The definitions were modeled after the Mycoses Study Group Criteria *[see References (15)].* Patients

were administered a single 70-mg loading dose of CANCIDAS and subsequently dosed with 50 mg daily. The mean duration of therapy was 33.7 days, with a range of 1 to 162 days.

An independent expert panel evaluated patient data, including diagnosis of invasive aspergillosis, response and tolerability to previous antifungal therapy, treatment course on CANCIDAS, and clinical outcome.

A favorable response was defined as either complete resolution (complete response) or clinically meaningful improvement (partial response) of all signs and symptoms and attributable radiographic findings. Stable, nonprogressive disease was considered to be an unfavorable response.

Among the 69 patients enrolled in the study, 63 met entry diagnostic criteria and had outcome data; and of these, 52 patients received treatment for >7 days. Fifty-three (84%) were refractory to previous antifungal therapy and 10 (16%) were intolerant. Forty-five patients had pulmonary disease and 18 had extrapulmonary disease. Underlying conditions were hematologic malignancy (N=24), allogeneic bone marrow transplant or stem cell transplant (N=18), organ transplant (N=8), solid tumor (N=3), or other conditions (N=10). All patients in the study received concomitant therapies for their other underlying conditions. Eighteen patients received tacrolimus and CANCIDAS concomitantly, of whom 8 also received mycophenolate mofetil.

Overall, the expert panel determined that 41% (26/63) of patients receiving at least one dose of CANCIDAS had a favorable response. For those patients who received >7 days of therapy with CANCIDAS, 50% (26/52) had a favorable response. The favorable response rates for patients who were either refractory to or intolerant of previous therapies were 36% (19/53) and 70% (7/10), respectively. The response rates among patients with pulmonary disease and extrapulmonary disease were 47% (21/45) and 28% (5/18), respectively. Among patients with extrapulmonary disease, 2 of 8 patients who also had definite, probable, or possible CNS involvement had a favorable response. Two of these 8 patients had progression of disease and manifested CNS involvement while on therapy.

There is 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 has not been evaluated in concurrently controlled clinical studies, with other antifungal therapies.

14.5 Pediatric Patients

The safety and efficacy of CANCIDAS were evaluated in pediatric patients 3 months to 17 years of age in two prospective, multicenter clinical trials.

The first study, which enrolled 82 patients between 2 to 17 years of age, was a randomized, double-blind study comparing CANCIDAS (50 mg/m^2 IV once daily following a 70-mg/m^2 loading dose on Day 1 [not to exceed 70 mg daily]) to AmBisome (3 mg/kg IV daily) in a 2:1 treatment fashion (56 on caspofungin, 26 on AmBisome) as empirical therapy in pediatric patients with persistent fever and neutropenia. The study design and criteria for efficacy assessment were similar to the study in adult patients *[see Clinical Studies (14.1)].* Patients were stratified based on risk category (high-risk patients had undergone allogeneic stem cell transplantation or had relapsed acute leukemia). Twenty-seven percent of patients in both treatment groups were high risk. Favorable overall response rates of pediatric patients with persistent fever and neutropenia are presented in Table 17.

TABLE 17
Favorable Overall Response Rates of Pediatric Patients with Persistent Fever and Neutropenia

	CANCIDAS	AmBisome*
Number of Patients	56	25
Overall Favorable Response	26/56 (46.4%)	8/25 (32.0%)
High risk	9/15 (60.0%)	0/7 (0.0%)
Low risk	17/41 (41.5%)	8/18 (44.4%)

*One patient excluded from analysis due to no fever at study entry.

The second study was a prospective, open-label, non-comparative study estimating the safety and efficacy of caspofungin in pediatric patients (ages 3 months to 17 years) with candidemia and other *Candida* infections, esophageal candidiasis, and invasive aspergillosis (as salvage therapy). The study employed diagnostic criteria which were based on established EORTC/MSG criteria of proven or probable infection; these criteria were similar to those criteria employed in the adult studies for these various indications. Similarly, the efficacy time points and endpoints used in this study were similar to those employed in the corresponding adult studies *[see Clinical Studies (14.2), (14.3), and (14.4)].* All

patients received CANCIDAS at 50 mg/m^2 IV once daily following a 70-mg/m^2 loading dose on Day 1 (not to exceed 70 mg daily). Among the 49 enrolled patients who received CANCIDAS, 48 were included in the efficacy analysis (one patient excluded due to not having a baseline *Aspergillus* or *Candida* infection). Of these 48 patients, 37 had candidemia or other *Candida* infections, 10 had invasive aspergillosis, and 1 patient had esophageal candidiasis. Most candidemia and other *Candida* infections were caused by *C. albicans* (35%), followed by *C. parapsilosis* (22%), *C. tropicalis* (14%), and *C. glabrata* (11%). The favorable response rate, by indication, at the end of caspofungin therapy was as follows: 30/37 (81%) in candidemia or other *Candida* infections, 5/10 (50%) in invasive aspergillosis, and 1/1 in esophageal candidiasis.

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16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

No. 3822 — CANCIDAS 50 mg is a white to off-white powder/cake for infusion in a vial with a red aluminum band and a plastic cap.

NDC 0006-3822-10 supplied as one single-use vial.

No. 3823 — 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.

NDC 0006-3823-10 supplied as one single-use vial.

Storage and Handling

Vials

The lyophilized vials should be stored refrigerated at 2° to 8°C (36° to 46°F).

Reconstituted Concentrate

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

Diluted Product

The final patient infusion solution in the IV bag or bottle can be stored at ≤25°C (≤77°F) for 24 hours or at 2 to 8°C (36 to 46°F) for 48 hours.

17 PATIENT COUNSELING INFORMATION

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.

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