PRODUCT MONOGRAPH

CANCIDAS®

Caspofungin for injection, 50 mg/vial, 70 mg/vial
(as caspofungin actetate)

Antifungal

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CANCIDAS®

Caspofungin for injection
(as caspofungin acetate)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous infusion	Powder for solution / 50 mg vial 70 mg vial	*For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

DESCRIPTION

CANCIDAS® (caspofungin acetate) 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 a member of a class of antifungal drugs (echinocandins) that inhibits the synthesis of β (1, 3)-D-glucan, an integral component of the fungal cell wall.

INDICATIONS AND CLINICAL USE

CANCIDAS® is indicated for use in adults and children 12 months and older for:

- Empirical therapy for presumed fungal infections in febrile, neutropenic patients (see CLINICAL TRIALS).
- Treatment of Invasive Candidiasis including candidemia, intra-abdominal abscesses, peritonitis and pleural space infections. CANCIDAS® has not been studied in *Candida* endocarditis, osteomyelitis or meningitis (see CLINICAL TRIALS).
- Treatment of Esophageal Candidiasis (see CLINICAL TRIALS).
- Treatment of Invasive Aspergillosis in patients who are refractory to or intolerant of other therapies. The indication is based on results from an open-label, non-comparative study that enrolled 69 adult patients with documented invasive aspergillosis refractory to or intolerant of other therapies. CANCIDAS® has not been studied as initial therapy for invasive aspergillosis (see CLINICAL TRIALS).

Geriatrics (≥ 65 years of age):
In a limited number of patients ≥ 65 years of age, no overall differences in safety or efficacy have been observed between elderly and younger patients.

Pediatrics (≤ 17 years of age):
The safety and effectiveness of CANCIDAS® in pediatric patients aged 12 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 12 months to 17 years of age (see CLINICAL TRIALS and DETAILED PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

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

The safety and efficacy of CANCIDAS® has not been adequately studied in neonates and infants under 3 months of age and children aged 3 to 11 months.

CONTRAINDICATIONS

CANCIDAS® is contraindicated in patients with hypersensitivity to any component of this product. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

Hypersensitivity
Anaphylaxis has been reported during administration of CANCIDAS®. If this occurs, CANCIDAS® should be discontinued and appropriate treatment administered.

Possible histamine-mediated adverse reactions, including rash, facial swelling, angioedema, pruritus, sensation of warmth, or bronchospasm have been reported and may require discontinuation and/or administration of appropriate treatment (see ADVERSE REACTIONS).

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported after post marketing use of caspofungin. Caution should apply in patients with history of allergic skin reactions (see **ADVERSE REACTIONS/ Post-Market Adverse Drug Reactions**).

Concomitant Use with Cyclosporine
Concomitant use of CANCIDAS® with cyclosporine should be limited to patients for whom the potential benefit outweighs the potential risk. Elevated liver function tests have been observed in 5 of 12 healthy adult subjects who received concomitant CANCIDAS® and cyclosporine (see

ADVERSE REACTIONS). 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 > 5 × upper limit of normal or > 3 × 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.

Hepatic Effects

Laboratory abnormalities in liver function tests have been seen in healthy volunteers and adult and pediatric patients treated with CANCIDAS®. In some adult and pediatric patients with serious underlying conditions who were receiving multiple concomitant medications with CANCIDAS®, 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 the risk/benefit of continuing CANCIDAS® therapy should be re-evaluated.

Special Populations

Pregnant Women: There are no adequate and well controlled studies in pregnant women. CANCIDAS® should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Caspofungin was shown to be embryotoxic in rats and rabbits. Findings included incomplete ossification of the skull and torso and an increased incidence of cervical rib in rats. An increased incidence of incomplete ossifications of the talus/calcaneus was seen in rabbits. Caspofungin also produced increases in resorptions in rats and rabbits and perimplantation losses in rats. These findings were observed at doses which produced exposures similar to those seen in patients treated with a 70 mg dose. Caspofungin crossed the placental barrier in rats and rabbits and was detected in the plasma of fetuses of pregnant animals dosed with CANCIDAS®.

Nursing Women: It is not known whether caspofungin is excreted in human milk. Caspofungin has been found in the milk of lactating laboratory animals. Women receiving CANCIDAS® should not breast-feed.

Pediatrics (≤ 17 years of age): The safety and effectiveness of CANCIDAS® in pediatric patients aged 12 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 12 months to 17 years of age (see CLINICAL TRIALS and DETAILED PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

The safety and efficacy of CANCIDAS® has not been adequately studied in neonates and infants under 3 months of age and children aged 3 to 11 months.

Postmarketing hepatobiliary adverse reactions have been reported in pediatric patients with serious underlying medical conditions (see WARNINGS AND PRECAUTIONS, Hepatic Effects).

Geriatrics (≥ 65 years of age): Clinical studies of CANCIDAS® did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In a limited number of patients ≥ 65 years of age, no overall differences in safety or efficacy have been observed between elderly and younger patients. Plasma concentrations of caspofungin in healthy older men and women (≥ 65 years of age) were increased slightly (approximately 28% in area under the curve [AUC]) compared to young healthy men. In patients who were treated empirically or who had invasive candidiasis, a similar modest effect of age was seen in older patients relative to younger patients. No dose adjustment is recommended for the elderly; however, greater sensitivity of some older individuals cannot be ruled out.

Patients with Special Diseases or Conditions

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. 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 (see DOSAGE AND ADMINISTRATION and DETAILED PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

Renal Insufficiency
Mild to advanced renal insufficiency does not alter significantly caspofungin plasma concentrations and does not require a change in dosing. Caspofungin is not dialyzable, thus supplementary dosing is not required following hemodialysis (see DETAILED PHARMACOLOGY, Renal Insufficiency).

ADVERSE REACTIONS

Hypersensitivity reactions have been reported (see WARNINGS AND PRECAUTIONS).

Adverse Drug Reaction Overview

Adverse Drug Reaction Overview from Clinical Trials in Adult Patients

In clinical studies, 1865 adult individuals received single or multiple doses of CANCIDAS®: 564 febrile, neutropenic patients (empirical therapy study), 382 patients with invasive 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 received chemotherapy for malignancy or had undergone hematopoietic stem-cell transplantation. 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 [with CD4 counts less than 50/mm^3]) requiring multiple concomitant medications. Patients in the noncomparative *Aspergillus* study 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.

Reported drug-related clinical and laboratory abnormalities among all adults treated with CANCIDAS® (total 1780) were typically mild and rarely led to discontinuation.

Common (> 1/100)	General	Fever, headache, chills, abdominal pain, pain
	GI	Nausea, diarrhea, vomiting
	Liver	Elevated liver enzyme levels (AST, ALT, alkaline phosphatase, direct and total bilirubin)
	Kidney	Increased serum creatinine
	Blood	Anemia (decreased hemoglobin and hematocrit)
	Cardiac	Tachycardia
	Metabolism	Hypokalaemia (blood potassium decreased)
	Peripheral Vascular	Phlebitis/thrombophlebitis, infusion-site pruritus, infused-vein complication, flushing.
	Bone	Arthralgia
	Respiratory	Dyspnea
	Skin	Rash, pruritus, sweating, erythema

Adverse Drug Reaction Overview from Clinical Trials in Pediatric Patients

In clinical studies, 171 pediatric patients received single or multiple doses of CANCIDAS®: 104 febrile, neutropenic patients; 56 patients with invasive candidiasis; 1 patient with esophageal candidiasis; and 10 patients with invasive aspergillosis. The overall clinical safety profile of CANCIDAS® in pediatric patients is comparable to that in adult patients.

Reported drug-related clinical and laboratory abnormalities among all pediatric patients treated with CANCIDAS® (total 171) were typically mild and rarely led to discontinuation.

Common	General	Fever, headache, chills
(> 1/100)	Liver	Elevated liver enzyme levels (AST, ALT)
	Cardiac	Tachycardia
	Peripheral Vascular	Catheter site pain, flushing, hypotension
	Skin	Rash, pruritus

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Clinical Trial Experience in Adult Patients

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§ (amphotericin B liposome for injection) (3.0 mg/kg/day). Drug-related clinical adverse experiences occurring in ≥ 2% of the patients in either treatment group are presented in Table 1.

TABLE 1
Drug-Related* Clinical Adverse Experiences Among Patients with Persistent Fever and Neutropenia Incidence ≥ 2% for at Least One Treatment Group by Body System

	CANCIDAS® 50 mg N=564 % (n)**	**AmBisome§ 3 mg/kg*** N=547 % (n)**
Clinical Adverse Experiences	47.0 (265)	59.6 (326)
Body as a Whole		
Fever	17.0 (96)	19.4 (106)
Chills	13.8 (78)	24.7 (135)
Perspiration/Diaphoresis	2.8 (16)	2.2 (12)
Flushing	1.8 (10)	4.2 (23)
Abdominal Pain	1.4 (8)	2.4 (13)
Cardiovascular System		
Tachycardia	1.4 (8)	2.4 (13)
Hypertension	1.1 (6)	2.0 (11)
Digestive System		
Nausea	3.5 (20)	11.3 (62)
Vomiting	3.5 (20)	8.6 (47)
Diarrhea	2.7 (15)	2.4 (13)
Metabolism and Nutrition		
Hypokalemia	3.7 (21)	4.2 (23)
Musculoskeletal System		
Back Pain	0.7 (4)	2.7 (15)
Nervous System & Psychiatric		
Headache	4.3 (24)	5.7 (31)

	CANCIDAS® 50 mg** N=564 % (n)	AmBisome§ 3 mg/kg*** N=547 % (n)
Respiratory System		
Dyspnea	2.0 (11)	4.2 (23)
Tachypnea	0.4 (2)	2.0 (11)
Skin & Skin Appendage		
Rash	6.2 (35)	5.3 (29)

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

The proportion of patients with drug-related clinical adverse experiences was higher in the AmBisome§ group (59.6%) than in the CANCIDAS® group (47.0%). Only rash, perspiration, and diarrhea were numerically higher in the CANCIDAS® group with the remaining adverse experiences being numerically higher in the AmBisome§ group. Numerically higher frequencies of clinical adverse experiences were observed in the CANCIDAS® group compared with the AmBisome§ group for serious rash (4 vs 0), discontinuations due to drug-related adverse experiences in the skin/skin appendages (10 vs 3), discontinuations due to drug-related hepatobiliary adverse events (4 vs 0).

Also reported was an isolated, serious adverse experience of hyperbilirubinemia considered possibly related to CANCIDAS®.

Infusion-related Reactions

The proportion of patients who experienced an infusion-related adverse event was significantly lower ($p < 0.001$) in the group treated with CANCIDAS® (35.1%) than in the group treated with AmBisome§ (51.6%).

The frequency of severe infusion-related fever was higher in the CANCIDAS® group compared with the AmBisome§ group (12 vs 6). However, the frequency of moderate or severe infusion-related fever was lower in the CANCIDAS® group than in the AmBisome§ group (61 vs 76).

Invasive Candidiasis

In an initial 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. Drug-related clinical adverse experiences occurring in ≥ 2% of the patients in either treatment group are presented in Table 2.

TABLE 2
Drug-Related* Clinical Adverse Experiences Among Patients with Invasive Candidiasis Incidence ≥ 2% for at Least One Treatment Group by Body System

	CANCIDAS® 50 mg** (n=114) % (n)	Amphotericin B 0.6-1.0 mg/kg (n=125) % (n)
Body as a Whole		
Fever	7.0 (8)	23.2 (29)
Chills	5.3 (6)	26.4 (33)

	CANCIDAS® 50 mg** (n=114) % (n)	Amphotericin B 0.6-1.0 mg/kg (n=125) % (n)
Cardiovascular System		
Hypertension	1.8 (2)	6.4 (8)
Tachycardia	1.8 (2)	10.4(13)
Hypotension	0.9 (1)	2.4 (3)
Peripheral Vascular System		
Phlebitis/thrombophlebitis	3.5 (4)	4.8 (6)
Digestive System		
Vomiting	3.5 (4)	8.0 (10)
Diarrhea	2.6 (3)	0.8 (1)
Nausea	1.8 (2)	5.6 (7)
Jaundice	0.9 (1)	3.2 (4)
Metabolic/Nutritional/Immune		
Hypokalemia	0.9 (1)	5.6 (7)
Nervous System & Psychiatric		
Tremor	1.8 (2)	2.4 (3)
Respiratory System		
Tachypnea	0	10.4 (13)
Skin & Skin Appendage		
Rash	0.9 (1)	3.2 (4)
Sweating	0.9 (1)	3.2 (4)
Erythema	0	2.4 (3)
Urogenital System		
Renal insufficiency	0.9 (1)	5.6 (7)
Renal insufficiency, acute	0	5.6 (7)

* Determined by the investigator to be possibly, probably, or definitely drug related.
** Patients received CANCIDAS® 70 mg on Day 1, then 50 mg daily for the remainder of their treatment.

The incidence of drug-related clinical adverse experiences was significantly lower among patients treated with CANCIDAS® (28.9%) than among patients treated with amphotericin B (58.4%). Also, the proportion of patients who experienced an infusion-related adverse event was significantly lower in the CANCIDAS® group (20.2%) than in the amphotericin B group (48.8%).

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. Drug-related clinical adverse experiences occurring in ≥ 2.0% of the patients in either treatment group are presented in Table 3. In addition, 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. In this study, three (3.0%) patients in the 150 mg group and none in the 70/50-mg group had at least one serious drug-related adverse experience (toxic hepatitis, leukopenia, and hyperbilirubinemia).

TABLE 3
Drug-Related* Clinical Adverse Experiences Among Patients with Invasive Candidiasis Incidence ≥ 2.0% for at Least One Treatment Group by System Organ Class or Preferred Term

Adverse Experience (MedDRA v11.0 System Organ Class and Preferred Term)	CANCIDAS® 50 mg† N=104 (percent)	CANCIDAS® 150 mg N=100 (percent)

Adverse Experience (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 Experience	**13.5**	**14.0**
General Disorders and Administration Site Conditions	**6.7**	**7.0**
Injection site erythema	0.0	2.0
Injection site phlebitis	3.8	2.0
Injection site swelling	1.0	2.0
Metabolism and Nutrition Disorders	**1.9**	**2.0**
Hypokalemia	1.0	2.0
Nervous System Disorders	**0.0**	**2.0**
Headache	0.0	2.0

* Determined by the investigator to be possibly, probably, or definitely drug-related. Within any system organ class, individuals may experience more than 1 adverse experience.

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

Esophageal and/or Oropharyngeal Candidiasis

Drug-related clinical adverse experiences occurring in ≥ 2% of patients with esophageal and/or oropharyngeal candidiasis are presented in Table 4.

TABLE 4
Drug-related* Clinical Adverse Experiences Among Patients with Esophageal and/or Oropharyngeal Candidiasis
Incidence ≥ 2% for at least one treatment dose (per comparison) by Body System

	CANCIDAS® 50 mg (N=83) % (n)**	**Fluconazole 200 mg** (N=94) % (n)**	**CANCIDAS® 50 mg*** (N=80) % (n)**	**CANCIDAS® 70 mg*** (N=65) % (n)**	**Amphotericin B 0.5 mg/kg*** (N=89) % (n)**
Body as a Whole					
Fever	3.6 (3)	1.1 (1)	21.3 (17)	26.2 (17)	69.7 (62)
Pain, abdominal	3.6 (3)	2.1 (2)	2.5 (2)	†	9.0 (8)
Chills	†	†	2.5 (2)	1.5 (1)	75.3 (67)
Pain	†	†	1.3 (1)	4.6 (3)	5.6 (5)
Edema, facial	†	†	†	3.1 (2)	†
Flu-like illness	†	†	†	3.1 (2)	†
Warm sensation	†	†	†	1.5 (1)	4.5 (4)
Asthenia/fatigue	†	†	†	†	6.7 (6)
Malaise	†	†	†	†	5.6 (5)
Edema/swelling	†	†	†	†	5.6 (5)
Cardiovascular System					
Tachycardia	†	†	1.3 (1)	†	4.5 (4)
Vasculitis	†	†	†	†	3.4 (3)
Peripheral Vascular					
Phlebitis/thrombophlebitis	15.7 (13)	8.5 (8)	11.3 (9)	13.8 (9)	22.5 (20)
Infused vein complication	12.0 (10)	8.5 (8)	2.5 (2)	1.5 (1)	†
Digestive System					
Nausea	6.0 (5)	6.4 (6)	2.5 (2)	3.1 (2)	21.3 (19)
Diarrhea	3.6 (3)	2.1 (2)	1.3 (1)	3.1 (2)	11.2 (10)
Vomiting	1.2 (1)	3.2 (3)	1.3 (1)	3.1 (2)	13.5 (12)
Anorexia	†	†	1.3 (1)	†	3.4 (3)
Gastritis	†	2.1 (2)	†	†	†
Musculoskeletal System					

	CANCIDAS® 50 mg** (N=83) % (n)	Fluconazole 200 mg** (N=94) % (n)	CANCIDAS® 50 mg*** (N=80) % (n)	CANCIDAS® 70 mg*** (N=65) % (n)	Amphotericin B 0.5 mg/kg*** (N=89) % (n)
Myalgia	1.2 (1)	†	†	3.1 (2)	2.2 (2)
Pain, back	†	†	†	†	2.2 (2)
Pain, musculoskeletal	†	†	1.3 (1)	†	4.5 (4)
Hemic & Lymphatic System					
Anemia	†	†	3.8 (3)	†	9.0 (8)
Metabolic/Nutritional/Immune					
Anaphylaxis	†	†	†	†	2.2 (2)
Nervous System & Psychiatric					
Headache	6.0 (5)	1.1 (1)	11.3 (9)	7.7 (5)	19.1 (17)
Insomnia	1.2 (1)	†	†	†	2.2 (2)
Paresthesia	†	†	1.3 (1)	3.1 (2)	1.1 (1)
Dizziness	†	2.1(2)	†	1.5 (1)	1.1 (1)
Tremor	†	†	†	†	7.9 (7)
Respiratory System					
Tachypnea	†	†	1.3 (1)	†	4.5 (4)
Skin & Skin Appendage					
Pruritus	1.2 (1)	†	2.5 (2)	1.5 (1)	†
Erythema	1.2 (1)	†	1.3 (1)	1.5 (1)	7.9 (7)
Rash	†	†	1.3 (1)	4.6 (3)	3.4 (3)
Sweating	†	†	1.3 (1)	†	3.4 (3)
Induration	†	†	†	3.1 (2)	6.7 (6)

* Relationship to drug was determined by the investigator to be possibly, probably, or definitely drug related. Patients who received CANCIDAS® 35 mg daily in these studies are not included in this table.
** Derived from a Phase III comparator-controlled clinical study.
*** Derived from Phase II comparator-controlled clinical studies.
† Incidence 0.0%

Invasive Aspergillosis

In the open-label, noncomparative aspergillosis study, in which patients received CANCIDAS® (70 mg loading dose on Day 1 followed by 50 mg daily), the following drug-related clinical adverse experiences were observed with an incidence of ≥ 2%: fever (2.9%), infused-vein complications (2.9%), nausea (2.9%), vomiting (2.9%) and flushing (2.9%).

Also reported in this patient population were pulmonary edema, adult respiratory distress syndrome (ARDS), and radiographic infiltrates.

Clinical Trial Experience in Pediatric Patients

The overall safety of caspofungin was assessed in 171 pediatric patients who received single or multiple doses of CANCIDAS®: 104 febrile, neutropenic patients; 56 patients with invasive candidiasis; 1 patient with esophageal candidiasis; and 10 patients with invasive aspergillosis. Table 5 shows the incidence of drug-related clinical adverse experiences reported in ≥ 2.0% of pediatric patients in clinical studies. The most common drug-related clinical adverse experiences in pediatric patients treated with CANCIDAS® were fever (11.7%), rash (4.7%), and headache (2.9%).

TABLE 5
Drug-Related* Clinical Adverse Experiences Among Pediatric Patients
Incidence ≥ 2% for at least one treatment dose by Body System

	CANCIDAS® Any Dose† N=171 (percent)	CANCIDAS® 50 mg/m²‡ N=56 (percent)	AmBisome§ 3 mg/kg‡ N=26 (percent)
Cardiac Disorders			
Tachycardia	1.2	1.8	11.5
Gastrointestinal Disorders			
Nausea	0.0	0.0	3.8
Vomiting	0.6	1.8	7.7
General Disorders & Administration Site Conditions			
Adverse Drug Reaction	0.0	0.0	3.8
Catheter Site Pain	1.2	3.6	0.0
Chills	1.8	1.8	7.7
Fever	11.7	28.6	23.1
Hepatobiliary Disorders			
Hepatitis, toxic	0.0	0.0	3.8
Hyperbilirubinemia	0.0	0.0	3.8
Jaundice	0.0	0.0	3.8
Metabolism & Nutrition Disorders			
Hypokalemia	0.6	0.0	3.8
Nervous System Disorders			
Headache	2.9	8.9	0.0
Respiratory, Thoracic, & Mediastinal Disorders			
Dyspnea	0.0	0.0	3.8
Laryngospasm	0.0	0.0	3.8
Skin & Subcutaneous Tissue Disorders			
Angioneurotic edema	0.0	0.0	3.8
Circumoral edema	0.0	0.0	3.8
Pruritus	1.8	3.6	0.0
Rash	4.7	8.9	0.0
Vascular Disorders			
Flushing	1.8	3.6	0.0
Hypotension	1.8	3.6	3.8

* Relationship to drug was determined by the investigator to be possibly, probably or definitely drug-related.
† Derived from all pediatric clinical studies.
‡ Derived from Phase II comparator-controlled clinical study of empirical therapy.

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

Laboratory Abnormalities

Laboratory Abnormalities in Adult Patients

Empirical Therapy

Drug-related laboratory adverse experiences occurring in ≥ 2% of the patients in either treatment group are presented in Table 6.

TABLE 6
Drug-Related* Laboratory Adverse Experiences Among Patients with Persistent Fever and Neutropenia Incidence ≥ 2% for at Least One Treatment Group by Laboratory Test Category

	CANCIDAS® 50 mg** N=564 % (n)†	AmBisome§ 3.0 mg/kg*** N=547 % (n)†
Drug Related Laboratory Abnormalities	22.5 (127)	32.0 (175)
Blood Chemistry		
Alanine aminotransferase increased	8.7 (49)	8.9 (48)
Alkaline phosphatase increased	7.0 (39)	12.0 (65)
Aspartate aminotransferase increased	7.0 (39)	7.6 (41)
Direct serum bilirubin increased	2.6 (10)	5.2 (20)
Total serum bilirubin increased	3.0 (17)	5.2 (28)
Hypokalemia	7.3 (41)	11.8 (64)
Hypomagnesemia	2.3 (12)	2.6 (13)
Serum creatinine increased	1.2 (7)	5.5 (30)

* Determined by the investigator to be possibly, probably, or definitely drug-related.
** 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.
† Not all tests were conducted for some patients.

The proportion of patients with drug-related laboratory adverse experiences was higher in the AmBisome§ group (32.0%) than in the CANCIDAS® group (22.5%). Each drug-related laboratory adverse experience with a frequency of ≥ 2% in at least one treatment group was numerically higher in the AmBisome§ group than in the CANCIDAS® group.

Numerically higher frequencies of clinically significant laboratory abnormalities were observed in the CANCIDAS® group compared with the AmBisome§ group for increased AST > 2.5 × ULN (9.7% vs 5.1%), increased AST > 2.5 × baseline (30.0% vs 27.9%); and increased ALT > 2.5 × baseline (30.4% vs 27.6%). Numerically lower frequencies of clinically significant laboratory abnormalities were observed in the CANCIDAS® group than the AmBisome§ group for increased alkaline phosphatase > 2.5 × ULN (6.5% vs 10.6%), increased alkaline phosphatase > 2.5 × baseline (10.6% vs 20.4%), and increased total bilirubin > 2.5 × ULN (7.1% vs 9.7%). The frequencies of other clinically significant laboratory abnormalities were similar in the two groups.

Nephrotoxicity

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%).

Invasive Candidiasis

The incidence of drug-related laboratory adverse experiences in patients with invasive candidiasis was significantly lower among patients receiving CANCIDAS® (24.3%) than among patients receiving amphotericin B (54.0%).

Drug-related laboratory adverse experiences occurring in ≥ 2% of the patients in an initial invasive candidiasis study are presented in Table 7.

TABLE 7
Drug-Related* Laboratory Adverse Experiences Among Patients with Invasive Candidiasis
Incidence ≥ 2% for at Least One Treatment Group by Laboratory Test Category

	CANCIDAS® 50 mg (n=114) % (n)†**	**Amphotericin B 0.6-1.0 mg/kg (n=125) % (n)†**
Blood Chemistry		
ALT increased	3.7 (4)	8.1 (10)
AST increased	1.9 (2)	9.0 (11)
Blood urea increased	1.9 (2)	15.8 (19)
Direct serum bilirubin increased	3.8 (3)	8.4 (8)
Serum alkaline phosphatase increased	8.3 (9)	15.6 (19)
Serum bicarbonate decreased	0	3.6 (4)
Serum creatinine increased	3.7 (4)	22.6 (28)
Serum phosphate increased	0	2.7 (3)
Serum potassium decreased	9.9 (11)	23.4 (29)
Serum potassium increased	0.9 (1)	2.4 (3)
Total serum bilirubin increased	2.8 (3)	8.9 (11)
Hematology		
Hematocrit decreased	0.9 (1)	7.3 (9)
Hemoglobin decreased	0.9 (1)	10.5 (13)
Urinalysis		
Urine protein increased	0	3.7 (4)

* Determined by the investigator to be possibly, probably, or definitely drug related.
** Patients received CANCIDAS® 70 mg on Day 1, then 50 mg daily for the remainder of their treatment.
† Not all tests were conducted for some patients.

The percentage of patients with either a drug-related clinical adverse experience or a drug-related laboratory adverse experience was significantly lower among patients receiving CANCIDAS® (42.1%) than among patients receiving amphotericin B (75.2%). Furthermore, a significant difference between the two treatment groups was observed with regard to incidence of discontinuation due to drug-related clinical or laboratory adverse experience; incidences were 3/114 (2.6%) in the CANCIDAS® group and 29/125 (23.2%) in the amphotericin B group.

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 CANCIDAS® group than in the amphotericin B group.

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. Drug-related laboratory adverse experiences occurring in ≥ 2.0% of the patients in either treatment group are presented in Table 8.

TABLE 8
Drug-Related* Laboratory Adverse Experiences Among Patients with Invasive Candidiasis
Incidence ≥ 2.0% for at Least One Treatment Group by System Organ Class or Preferred Term

Adverse Experience (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 Experience	**7.8**	**7.1**
Alanine Aminotransferase increased	2.0	2.0
Alkaline Phosphatase increased	6.9	2.0
Aspartate Aminotransferase increased	4.0	2.0

* Determined by the investigator to be possibly, probably, or definitely drug-related. Within any system organ class, individuals may experience more than 1 adverse experience

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

Esophageal and/or Oropharyngeal Candidiasis

Drug-related laboratory abnormalities occurring in ≥ 2% of patients with esophageal and/or oropharyngeal candidiasis are presented in Table 9.

TABLE 9
Drug-related* Laboratory Abnormalities Reported Among Patients with Esophageal and/or Oropharyngeal Candidiasis
Incidence ≥ 2% (for at least one treatment dose) by Laboratory Test Category

	CANCIDAS® 50 mg** (N=163) % (n)††	CANCIDAS® 70 mg*** (N=65) % (n)††	Fluconazole 200 mg** (N=94) % (n)††	Amphotericin B 0.5 mg/Kg*** (N=89) % (n)††
Blood Chemistry				
ALT increased	10.6 (17)	10.8 (7)	11.8 (11)	22.7 (20)
AST increased	10.5 (17)	10.8 (7)	12.9 (12)	22.7 (20)
Blood urea increased	†	†	1.2 (1)	10.3 (9)
Direct serum bilirubin increased	0.6 (1)	†	3.3 (3)	2.5 (2)
Serum albumin decreased	8.6 (14)	4.6 (3)	5.4 (5)	14.9 (13)
Serum alkaline phosphatase increased	10.5 (17)	7.7 (5)	11.8 (11)	19.3 (17)
Serum bicarbonate decreased	0.9 (1)	†	†	6.6 (4)
Serum calcium decreased	1.9 (3)	†	3.2 (3)	1.1 (1)
Serum creatinine increased	†	1.5 (1)	2.2 (2)	28.1 (25)
Serum potassium decreased	3.7 (6)	10.8 (7)	4.3 (4)	31.5 (28)
Serum potassium increased	0.6 (1)	†	2.2 (2)	1.1 (1)
Serum sodium decreased	1.9 (3)	1.5 (1)	3.2 (3)	1.1 (1)
Serum uric acid increased	0.6 (1)	†	†	3.4 (3)
Total serum bilirubin increased	†	†	3.2 (3)	4.5 (4)
Total serum protein decreased	3.1 (5)	†	3.2 (3)	3.4 (3)

	CANCIDAS® 50 mg** (N=163) % (n)††	CANCIDAS® 70 mg*** (N=65) % (n)††	Fluconazole 200 mg** (N=94) % (n)††	Amphotericin B 0.5 mg/Kg*** (N=89) % (n)††
Hematology				
Eosinophils increased	3.1 (5)	3.1 (2)	1.1 (1)	1.1 (1)
Hematocrit decreased	11.1 (18)	1.5 (1)	5.4 (5)	32.6 (29)
Hemoglobin decreased	12.3 (20)	3.1 (2)	5.4 (5)	37.1 (33)
Lymphocytes increased	†	1.6 (1)	2.2 (2)	†
Neutrophils decreased	1.9 (3)	3.1 (2)	3.2 (3)	1.1 (1)
Platelet count decreased	3.1 (5)	1.5 (1)	2.2 (2)	3.4 (3)
Prothrombin time increased	1.3 (2)	1.5 (1)	†	2.3 (2)
WBC count decreased	6.2 (10)	4.6 (3)	8.6 (8)	7.9 (7)
Urinalysis				
Urine blood increased	†	†	†	4.0 (2)
Urine casts increased	†	†	†	8.0 (4)
Urine pH increased	0.8 (1)	†	†	3.6 (2)
Urine protein increased	1.2 (2)	†	3.3 (3)	4.5 (4)
Urine RBC's increased	1.1 (1)	3.8 (1)	5.1 (4)	12.0 (6)
Urine WBC's increased	†	7.7 (2)	†	24.0 (12)

* Relationship to drug was determined by the investigator to be possibly, probably, or definitely drug-related. Patients who received CANCIDAS® 35 mg daily in these studies are not included in this table.

** Derived from Phase II and Phase III comparator-controlled clinical studies.

*** Derived from Phase II comparator-controlled studies.

† Incidence 0.0%

†† Not all tests were conducted for some patients.

Invasive Aspergillosis

Drug-related laboratory abnormalities reported with an incidence ≥ 2% in patients treated with CANCIDAS® in the noncomparative aspergillosis study were: serum alkaline phosphatase increased (2.9%), serum potassium decreased (2.9%), eosinophils increased (3.2%), urine protein increased (4.9%), and urine RBCs increased (2.2%).

Concomitant Therapy with Cyclosporine

In one clinical study, 3 of 4 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 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 2 × 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).

Laboratory Abnormalities in Pediatric Patients

Table 10 shows the incidence of drug-related laboratory adverse experiences reported in ≥ 2.0% of pediatric patients in clinical studies. The overall laboratory safety profile in pediatric patients is comparable to that in adult patients. The most common drug-related laboratory adverse experiences in pediatric patients treated with CANCIDAS® were increased ALT (6.5%) and increased AST (7.6%).

TABLE 10
Drug-Related* Laboratory Adverse Experiences Among Pediatric Patients
Incidence ≥ 2% for at least one treatment dose by Body System

	CANCIDAS® Any Dose† N=171 (percent)	CANCIDAS® 50 mg/m²‡ N=56 (percent)	AmBisome§ 3 mg/kg‡ N=26 (percent)
Blood Chemistry Test			
ALT increased	6.5	3.6	0.0
AST increased	7.6	1.8	0.0
Blood bilirubin increased	0.6	1.8	4.0
Blood phosphorus decreased	2.0	1.8	0.0
Blood potassium decreased	3.5	3.6	11.5
Blood sodium decreased	0.0	0.0	3.8
Direct bilirubin increased	0.0	0.0	6.3

* Relationship to drug was determined by the investigator to be possibly, probably or definitely drug-related.
† Derived from all pediatric clinical studies.
‡ Derived from Phase II comparator-controlled clinical study of empirical therapy.

None of the patients receiving CANCIDAS® or AmBisome§ developed a serious drug-related adverse event or were discontinued from therapy due to a drug-related laboratory adverse experience.

Overall Safety Experience of CANCIDAS® in Clinical Trials

The overall safety of CANCIDAS® was assessed in 2036 individuals (including 1642 adult or pediatric patients and 394 volunteers) from 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 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 11.

Overall, 1665 of the 1951 (85.3%) patients/volunteers who received CANCIDAS® experienced an adverse reaction.

TABLE 11
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)	
	N	(%)
All Systems, Any Adverse Reaction	**1665**	**(85.3)**
Investigations	**901**	**(46.2)**
Alanine Aminotransferase Increased	258	(13.2)
Aspartate Aminotransferase Increased	233	(11.9)
Blood Alkaline Phosphatase Increased	232	(11.9)
Blood Potassium Decreased	220	(11.3)
Blood Bilirubin Increased	117	(6.0)
General Disorders and Administration Site Conditions	**843**	**(43.2)**
Pyrexia	381	(19.5)
Chills	192	(9.8)
Edema Peripheral	110	(5.6)
Gastrointestinal Disorders	**754**	**(38.6)**
Diarrhea	273	(14.0)
Nausea	166	(8.5)
Vomiting	146	(7.5)
Abdominal Pain	112	(5.7)
Infections and Infestations	**730**	**(37.4)**
Pneumonia	115	(5.9)
Respiratory, Thoracic, and Mediastinal Disorders	**613**	**(31.4)**
Cough	111	(5.7)
Skin and Subcutaneous Tissue Disorders	**520**	**(26.7)**
Rash	159	(8.1)
Erythema	98	(5.0)
Nervous System Disorders	**412**	**(21.1)**
Headache	193	(9.9)
Vascular Disorders	**344**	**(17.6)**
Hypotension	118	(6.0)

* 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.

Clinical Trial Adverse Drug Reactions (< 5%)

Clinically significant adverse reactions, regardless of causality or incidence which occurred in these trials, are listed below.

Blood and Lymphatic System Disorders: anaemia, 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

Immune System Disorders: bacteremia, sepsis, urinary tract infection

Metabolism and Nutrition Disorders: anorexia, decreased appetite, fluid overload, hypomagnesemia, hypercalcemia, hyperglycemia, hypokalemia

Musculoskeletal and Connective Tissue 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

Post-Market Adverse Drug Reactions

In addition to adverse events identified in clinical trials, the following events have been identified since market introduction of CANCIDAS®. Because they are reported spontaneously from a population of unknown size, estimates of frequency cannot be made. The following events have been chosen for inclusion due to their seriousness, frequency of reporting, potential causal connection to CANCIDAS®, or a combination of these factors.

The following post-marketing adverse events have been reported:

Allergic and immune system disorders: angioedema

Gastrointestinal disorders: pancreatitis

Hepatobiliary disorders: hepatic necrosis, rare cases of hepatic dysfunction

Metabolism and nutrition disorders: hypercalcemia

Investigations: gamma-glutamyltransferase increased

Renal and urinary disorders: clinically significant renal dysfunction

Skin and subcutaneous tissue disorders: erythema multiforme, Stevens-Johnson syndrome, skin exfoliation, toxic epidermal necrolysis

General disorders and administration site conditions: swelling and peripheral edema

Postmarketing hepatobiliary adverse reactions have been reported in pediatric patients with serious underlying medical conditions (see WARNINGS AND PRECAUTIONS, Hepatic Effects).

DRUG INTERACTIONS

Overview

Studies *in vitro* show that caspofungin acetate is not an inhibitor of any enzyme in the cytochrome P450 (CYP) system at or up to 5 times the concentration expected in human use. 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.

Studies in healthy adult volunteers show that the pharmacokinetics of caspofungin are not significantly altered by itraconazole, amphotericin B, mycophenolate, nelfinavir or tacrolimus. Caspofungin has no significant effect on the pharmacokinetics of itraconazole, amphotericin B, rifampin or the active metabolite of mycophenolate.

Drug-Drug Interactions

Tacrolimus

For adult patients receiving both caspofungin and tacrolimus, standard monitoring of tacrolimus blood concentrations and appropriate tacrolimus dosage adjustments are recommended. Caspofungin reduced the blood AUC of tacrolimus by approximately 20%, maximal 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.

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 and ADVERSE REACTIONS).

Rifampin

Results from two clinical drug interaction studies in healthy adult volunteers indicate that rifampin both induces and inhibits caspofungin disposition with net induction at steady state. In one study, rifampin and caspofungin were co-administered for 14 days with both therapies initiated on the same day. In the second study, rifampin was administered alone for 14 days to allow the induction effect to reach steady state, and then rifampin and caspofungin were co-

administered for an additional 14 days. When the induction effect of rifampin was at steady state, there was little change in caspofungin AUC or end-of-infusion concentration, but caspofungin trough concentrations were reduced by approximately 30%. The inhibitory effect of rifampin was demonstrated when rifampin and caspofungin treatments were initiated on the same day, and a transient elevation in caspofungin plasma concentrations occurred on Day 1 (approximately 60% increase in AUC). This inhibitory effect was not seen when caspofungin was added to preexisting rifampin therapy, and no elevation in caspofungin concentrations occurred. When CANCIDAS® is co-administered to adult patients with rifampin (or other inducers of drug clearance - see Other Medications), use of a daily dose of 70 mg of CANCIDAS® may be considered (see DOSAGE AND ADMINISTRATION).

Other Medications
Results from population pharmacokinetic screening in adults suggests that co-administration of inducers of drug clearance (efavirenz, nevirapine, phenytoin, dexamethasone or carbamazepine) with CANCIDAS® may result in clinically meaningful reductions in caspofungin concentrations. Available data suggest that the inducible drug clearance mechanism involved in caspofungin disposition is likely an uptake transport process, rather than metabolism. Therefore, when CANCIDAS® is co-administered to adult patients with inducers of drug clearance, such as efavirenz, nevirapine, rifampin, dexamethasone, phenytoin, or carbamazepine, use of a daily dose of 70 mg of CANCIDAS® may be considered (see DOSAGE AND ADMINISTRATION).

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.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbs have not been established.

Drug-Laboratory Test Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Do not mix or co-infuse CANCIDAS® with other medications. 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.

CANCIDAS® should be administered by slow intravenous infusion over approximately 1 hour.

Recommended Dose and Dosage Adjustment in Adult Patients

Empirical Therapy for Presumed Fungal Infections in Febrile, Neutropenic Patients

A single 70 mg loading dose should be administered on Day 1, followed by 50 mg daily thereafter. CANCIDAS® should be administered by slow intravenous infusion over approximately 1 hour. 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.

Invasive Candidiasis

A single 70 mg loading dose should be administered on Day 1, followed by 50 mg daily thereafter. CANCIDAS® should be administered by slow intravenous infusion over approximately 1 hour. Duration of treatment of invasive candidiasis 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

Fifty (50) mg should be administered daily by slow intravenous infusion over approximately 1 hour. Duration of treatment should be dictated by the patient's clinical response. Because of the risk of relapse of oropharyngeal candidiasis in HIV-infected patients with esophageal and/or oropharyngeal candidiasis at baseline, suppressive oral therapy could be considered (see CLINICAL TRIALS). 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. CANCIDAS® should be administered by slow intravenous infusion over approximately 1 hour. 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 efficacy of doses above 70 mg has not been adequately studied in patients with invasive aspergillosis.

Adult Patients Receiving Concomitant Inducers of Drug Clearance

When CANCIDAS® is co-administered with inducers of drug clearance, such as efavirenz, nevirapine, rifampin, dexamethasone, phenytoin, or carbamazepine, use of a daily dose of 70 mg of CANCIDAS® may be considered (see DRUG INTERACTIONS).

No dosage adjustment is necessary for elderly patients (65 years of age or older).

No dosage adjustment is necessary based on gender, race, or renal impairment.

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. 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 (see DETAILED PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

Recommended Dose and Dosage Adjustment in Pediatric Patients (≤ 17 years of age)
CANCIDAS® should be administered in pediatric patients by slow IV infusion over approximately 1 hour.

Dosing in pediatric patients (12 months to 17 years of age) should be based on the patient's body surface area (see DOSAGE AND ADMINISTRATION, Preparation of CANCIDAS® for Infusion in Pediatric Patients (≤ 17 years of age)). For all indications, a single 70 mg/m^2 loading dose (not to exceed an actual dose of 70 mg) should be administered on Day 1, followed by 50 mg/m^2 daily thereafter (not to exceed an actual dose of 70 mg daily). Duration of treatment should be individualized to the indication, as described for each indication in adults (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment in Adult Patients).

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 an actual daily dose of 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.

When CANCIDAS® is co-administered to pediatric patients with inducers of drug clearance, such as rifampin, efavirenz, nevirapine, phenytoin, dexamethasone, or carbamazepine, use of a CANCIDAS® dose of 70 mg/m^2 daily (not to exceed an actual daily dose of 70 mg) should be considered (see DRUG INTERACTIONS).

The efficacy and safety of CANCIDAS® have not been adequately studied in neonates and infants under 3 months of age and children aged 3 to 11 months.

Missed Dose
The injection schedule will be set by the physician, who will monitor the response and condition to determine what treatment is needed.

Administration

DIRECTIONS FOR RECONSTITUTION AND DILUTION

Preparation of CANCIDAS® for Infusion in Adults

Preparation of the 70 mg Day 1 loading-dose infusion for adults

1. Equilibrate the refrigerated vial of CANCIDAS® to room temperature.

2. Aseptically add 10.5 mL of either 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[a]. Do not mix with diluents containing dextrose (α-D-glucose) as CANCIDAS® is not stable in diluents containing dextrose. This reconstituted solution may be stored for up to 1 hour at 15°C to 25°C.[b]

3. Aseptically transfer 10 mL[c] of reconstituted CANCIDAS® to an IV bag (or bottle) containing 250 mL 0.9%, 0.45%, or 0.225% Sterile Saline for Injection, or Lactated Ringer's Injection. Do not mix with diluents containing dextrose (α-D-glucose) as CANCIDAS® is not stable in diluents containing dextrose. This infusion solution should be used without delay. It can, however, be stored for up to 24 hours at 15°C to 25°C or for 48 hours refrigerated at 2°C to 8°C. (If a 70 mg vial is unavailable, see below: **Alternative Infusion Preparation Methods, Preparation of 70 mg Day 1 loading dose from two 50 mg vials**).

Preparation of the daily 50 mg infusion for adults

1. Equilibrate the refrigerated vial of CANCIDAS® to room temperature.

2. Aseptically add 10.5 mL of either 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[a]. Do not mix with diluents containing dextrose (α-D-glucose) as CANCIDAS® is not stable in diluents containing dextrose. This reconstituted solution may be stored for up to 1 hour at 15°C to 25°C.[b]

3. Aseptically transfer 10mL[c] of reconstituted CANCIDAS® to an IV bag (or bottle) containing 250 mL 0.9%, 0.45%, or 0.225% Sterile Saline for Injection, or Lactated Ringer's Injection. Do not mix with diluents containing dextrose (α-D-glucose) as CANCIDAS® is not stable in diluents containing dextrose. This infusion solution should be used without delay. It can, however, be stored for up to 24 hours at 15°C to 25°C or 48 hours refrigerated at 2°C to 8°C. (If a reduced infusion volume is medically necessary, see below: **Alternative Infusion Preparation Methods, Preparation of 50 mg daily doses at reduced volume**).

Alternative Infusion Preparation Methods for adults

Preparation of 70 mg Day 1 loading dose from two 50 mg vials

Reconstitute two 50 mg vials with 10.5 mL of diluent each (see **Preparation of the daily 50 mg infusion**). Aseptically transfer a total of 14 mL of the reconstituted CANCIDAS® from the two vials to 250 mL 0.9%, 0.45%, or 0.225% Sterile Saline for Injection, or Lactated Ringer's Injection. Do not mix with diluents containing dextrose (α-D-glucose) as CANCIDAS® is not stable in diluents containing dextrose. This infusion solution should be used without delay. It can, however, be stored for up to 24 hours at 15°C to 25°C or 48 hours refrigerated at 2°C to 8°C.

Preparation of 50 mg daily doses at reduced volume for adults

When medically necessary, the 50 mg daily doses can be prepared by adding 10 mL of reconstituted CANCIDAS® to 100 mL of 0.9%, 0.45%, or 0.225% Sterile Saline for Injection, or Lactated Ringer's Injection. Do not mix with diluents containing dextrose (α-D-glucose) as CANCIDAS® is not stable in diluents containing dextrose. This infusion solution should be used without delay. It can, however, be stored for up to 24 hours at 15°C to 25°C or 48 hours refrigerated at 2°C to 8°C (see **Preparation of the daily 50 mg infusion**).

Preparation of a 35 mg daily dose from a 70 mg vial for adult patients with moderate hepatic insufficiency

Reconstitute one 70 mg vial (see above: **Preparation of the 70 mg Day 1 loading dose infusion**). Aseptically transfer 5 mL of the reconstituted CANCIDAS® from the vial to 250 mL or, if medically necessary, to 100 mL of 0.9%, 0.45%, or 0.225% Sterile Saline for Injection, or Lactated Ringer's Injection. Do not mix with diluents containing dextrose (α-D-glucose) as CANCIDAS® is not stable in diluents containing dextrose. This infusion solution should be used without delay. It can however, be stored for up to 24 hours at 15°C to 25°C or 48 hours refrigerated at 2°C to 8°C.

Preparation of a 35 mg daily dose from a 50 mg vial for adult patients with moderate hepatic insufficiency

Reconstitute one 50 mg vial (see above: **Preparation of the daily 50 mg infusion**). Aseptically transfer 7 mL of the reconstituted CANCIDAS® from the vial to 250 mL of 0.9%, 0.45%, or 0.225% Sterile Saline for Injection, or Lactated Ringer's Injection or, if medically necessary, to 100 mL of 0.9%, 0.45%, or 0.225% Sterile Saline for Injection, or Lactated Ringer's Injection. Do not mix with diluents containing dextrose (α-D-glucose) as CANCIDAS® is not stable in diluents containing dextrose. This infusion solution should be used without delay. It can, however, be stored for up to 24 hours at 15°C to 25°C or 48 hours refrigerated at 2°C to 8°C.

TABLE 12
Preparation of the Patient Infusion Solutions in Adults

DOSE*	Volume of reconstituted CANCIDAS® for transfer to intravenous bag or bottle	Typical preparation (reconstituted CANCIDAS® added to 250 mL)		Reduced volume infusion (reconstituted CANCIDAS® added to 100 mL)	
		Infusion Volume (mL)	Final Concentration (mg/mL)	Infusion Volume (mL)	Final Concentration (mg/mL)
70 mg	10 mL	260	0.28	not recommended	
70 mg (from two 50 mg vials)**	14 mL	264	0.28	not recommended	
50 mg	10 mL	260	0.20	110	0.47
35 mg for moderate hepatic insufficiency (from one 70 mg vial)	5 mL	255	0.14	105	0.34
35 mg for moderate hepatic insufficiency (from one 50 mg vial)	7 mL	257	0.14	107	0.34

* 10.5 mL should be used for reconstitution of all vials
** If a 70 mg vial is not available, the 70 mg dose can be prepared from two 50 mg vials.

Preparation of CANCIDAS® for Infusion in Pediatric Patients (≤ 17 years of age)

Calculation of Body Surface Area (BSA) for pediatric dosing

Before preparation of infusion, calculate the body surface area (BSA) of the patient using the following formula (Mosteller Formula):

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

Preparation of the 70 mg/m² infusion for pediatric patients ≥ 12 months of age (using a 70 mg vial)

1. Determine the actual loading dose to be used in the pediatric patient by using the patient's BSA (as calculated above) and the following equation:
   $$BSA\ (m^2) \times 70\ mg/m^2 = Loading\ Dose$$
   The maximum loading dose on Day 1 should not exceed 70 mg regardless of the patient's calculated dose.
2. Equilibrate the refrigerated vial of CANCIDAS® to room temperature.
3. Aseptically add 10.5 mL of 0.9% Sodium Chloride Injection, Sterile Water for Injection or Bacteriostatic Water for Injection with methylparaben and propylparaben.[a] This reconstituted solution may be stored for up to 1 hour at 15°C to 25°C.[b] This will give a final caspofungin concentration in the vial of 7.2 mg/mL.
4. Remove the volume of drug equal to the calculated loading dose (Step 1) from the vial. Aseptically transfer this volume (mL)[c] 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 Ringer's Injection. Alternatively, the volume (mL)[c] of reconstituted CANCIDAS® can be added to a reduced volume of 0.9%, 0.45%, or 0.225% Sodium Chloride Injection or Lactated Ringer's Injection, not to exceed a final concentration of 0.5 mg/mL. This infusion

solution should be used without delay. It can, however, be stored for up to 24 hours at 15°C to 25°C or 48 hours refrigerated at 2°C to 8°C.

5. If the calculated loading dose is < 50 mg, then the dose may be prepared from the 50 mg vial [follow Steps 2-4 from **Preparation of the 50 mg/m^2 infusion for pediatric patients ≥ 12 months of age (using a 50 mg vial)**]. The final caspofungin concentration in the 50 mg vial after reconstitution is 5.2 mg/mL.

Preparation of the 50 mg/m^2 infusion for pediatric patients ≥ 12 months of age (using a 50 mg vial)

1. Determine the daily maintenance dose to be used in the pediatric patient by using the patient's BSA (as calculated above) and the following equation:
   BSA (m^2) × 50 mg/m^2 = Daily Maintenance Dose
   The daily maintenance dose should not exceed 70 mg regardless of the patient's calculated dose.
2. Equilibrate the refrigerated vial of CANCIDAS® to room temperature.
3. Aseptically add 10.5 mL of 0.9% Sodium Chloride Injection, Sterile Water for Injection or Bacteriostatic Water for Injection with methylparaben and propylparaben.[a] This reconstituted solution may be stored for up to 1 hour at 15°C to 25°C.[b] This will give a final caspofungin concentration in the vial of 5.2 mg/mL.
4. Remove the volume of drug equal to the calculated loading dose (Step 1) from the vial. Aseptically transfer this volume (mL)[c] 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 Ringer's Injection. Alternatively, the volume (mL)[c] of reconstituted CANCIDAS® can be added to a reduced volume of 0.9%, 0.45%, or 0.225% Sodium Chloride Injection or Lactated Ringer's Injection, not to exceed a final concentration of 0.5 mg/mL. This infusion solution should be used without delay. It can, however, be stored for up to 24 hours at 15°C to 25°C or 48 hours refrigerated at 2°C to 8°C.
5. If the actual daily maintenance dose is > 50 mg, then the dose may be prepared from the 70 mg vial [follow Steps 2-4 from **Preparation of the 70 mg/m^2 infusion for pediatric patients ≥ 12 months of age (using a 70 mg vial)**]. The final caspofungin concentration in the 70 mg vial after reconstitution is 7.2 mg/mL.

Preparation notes:

a. The white to off-white compact powder will dissolve completely. Mix gently until a clear solution is obtained.
b. As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used.
c. CANCIDAS® is formulated to provide the full labeled vial dose (70 mg or 50 mg) when 10 mL is withdrawn from the vial.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

In clinical studies, the highest dose was 210 mg, which was administered as a single dose to 6 healthy adult subjects, and was generally well tolerated.

Caspofungin is not dialyzable.

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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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 a member of a class of antifungal drugs (echinocandins) that inhibits the synthesis of β (1, 3)-D-glucan, an integral component of the fungal cell wall.

Pharmacodynamics

Caspofungin acetate, inhibits the synthesis of β (1, 3)-D-glucan, an essential component of the cell wall of many filamentous fungi and yeast. β (1, 3)-D-glucan is not present in mammalian cells. Caspofungin has shown activity in regions of active cell growth of the hyphae of *Aspergillus fumigatus*.

Caspofungin has *in vitro* activity against various pathogenic fungi of the *Aspergillus* and *Candida* species.

Interpretive standards (or breakpoints) for caspofungin against *Candida* species are applicable only to tests performed using CLSI microbroth dilution reference method M27-A3 for minimum inhibitory concentrations (MIC) read as a partial inhibition endpoint at 24 hours. The MIC values for caspofungin using CLSI microbroth dilution reference method M27-A3 should be interpreted according to the criteria provided in Table 13 below (CLSI M27-S3).

TABLE 13
Susceptibility Interpretive Criteria for Caspofungin against *Candida* Species

Pathogen	Broth Microdilution MIC[*,†] (µg/mL) at 24 hours			
	Susceptible			**Non-susceptible**
Candida species	≤ 2			> 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.
[†] There is no Indeterminate or Resistant category assigned for the echinocandin agents; isolates with higher MICs (> 2 ug/mL) are categorized as Non-susceptible.

There are no established breakpoints for caspofungin against *Candida* species using the European Committee for Antimicrobial Susceptibility Testing (EUCAST) method.

Standardized techniques for susceptibility testing have been established for yeasts by EUCAST. No standardized techniques for susceptibility testing or interpretive breakpoints have been

established for *Aspergillus* species and other filamentous fungi using either the CLSI or EUCAST method.

Pharmacokinetics

Plasma concentrations of caspofungin decline in a polyphasic manner following single 1-hour intravenous infusions. A short α-phase occurs for 1 to 2 hours immediately post-infusion, followed by a β-phase with a half-life of 9 to 11 hours. An additional γ-phase also occurs with a half-life of 27 hours. Distribution, rather than excretion or biotransformation, is the dominant mechanism influencing plasma clearance. Approximately 75% of a radioactive dose was recovered: 41% in urine and 34% in feces. Caspofungin is slowly metabolized by hydrolysis and N-acetylation. Caspofungin also undergoes spontaneous chemical degradation to an open-ring peptide compound. At later time points (≥ 5 days post-dose), there is a low level (≤ 7 pmol/mg protein, or ≤ 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. There is little excretion or biotransformation of caspofungin during the first 30 hours after administration. Caspofungin is extensively bound to albumin (approximately 97%), and it is slowly metabolized by hydrolysis and N-acetylation. A small amount of caspofungin is excreted unchanged in urine (approximately 1.4% of dose). Renal clearance of parent drug is low (see DETAILED PHARMACOLOGY, Pharmacokinetics).

STORAGE AND STABILITY

Vials

The lyophilized single-dose vials should be stored at 2°C to 8°C. Discard unused portion.

Reconstituted Concentrate

Reconstituted CANCIDAS® may be stored at 15°C to 25°C for up to 1 hour prior to the preparation of the patient infusion solution.

Patient Infusion Solution

The final patient infusion solution in the IV bag or bottle should be used without delay. It can, however, be stored for up to 24 hours at 15°C to 25°C or up to 48 hours refrigerated at 2°C to 8°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

CANCIDAS® 50 mg is a white to off-white compact powder for infusion in a vial with a red aluminum seal and a plastic flip-off cap. Packaged as a single-dose vial in a carton.

Each 50 mg vial of CANCIDAS® contains 50 mg caspofungin as caspofungin acetate. Inactive ingredients: 39.0 mg sucrose, 26.0 mg mannitol and 2.0 mg glacial acetic acid. The pH may have been adjusted with acetic acid and/or sodium hydroxide.

CANCIDAS® 70 mg is a white to off-white compact powder for infusion in a vial with a yellow/orange aluminum seal and a plastic flip-off cap. Packaged as a single-dose vial in a carton.

Each 70 mg vial of CANCIDAS® contains 70 mg caspofungin as caspofungin acetate. Inactive ingredients: 54.0 mg sucrose, 36.0 mg mannitol and 2.7 mg glacial acetic acid. The pH may have been adjusted with acetic acid and/or sodium hydroxide.

CANCIDAS® does not contain any preservative agents.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

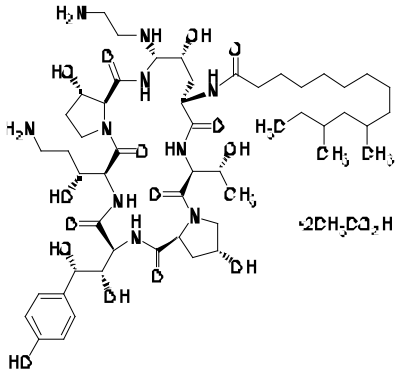
Proper name: caspofungin acetate

Chemical name: 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).

Molecular formula: $C_{52}H_{88}N_{10}O_{15}•2C_2H_4O_2$

Molecular mass: 1213.42

Structural formula:



Physicochemical properties:

Physical Form: Caspofungin acetate is a hygroscopic, white to off-white powder. It is freely soluble in water and methanol, and slightly soluble in ethanol.

pH: The pH of a saturated aqueous solution of caspofungin acetate is approximately 6.6.

CLINICAL TRIALS

The results of the adult clinical studies are presented by each indication below, followed thereafter by the results of pediatric clinical trials.

Adult Patients

Empirical Therapy in Febrile, Neutropenic Patients

A total of 1111 patients with persistent fever and neutropenia were enrolled in a clinical study and treated with either CANCIDAS® (caspofungin acetate) 50 mg once daily following a 70 mg loading dose or AmBisome§ 3.0 mg/kg/day. Eligible patients had received chemotherapy for malignancy or had undergone hematopoietic stem-cell transplantation, and presented with neutropenia for at least 96 hours (< 500 cells/mm3) and fever (> 38.0°C) not responding to at least 96 hours of antibacterial therapy. Patients were to be treated until resolution of neutropenia, with a maximum duration of 28 days. However, patients found to have a documented fungal infection could be treated longer. If the drug was well tolerated but the patient's fever persisted and clinical condition deteriorated after 5 days of therapy, the dosage of study drug could be increased to 70 mg/day of CANCIDAS® (13.3% of patients treated) or to 5.0 mg/kg/day of AmBisome§ (14.3% of patients treated). An overall favourable response required meeting each of 5 criteria: (1) successful treatment of any baseline fungal infection, (2) no breakthrough fungal infections during administration of study drug or within 7 days after completion of treatment, (3) survival for 7 days after completion of study therapy, (4) no discontinuation from the study drug because of drug-related toxicity or lack of efficacy, and (5) resolution of fever during the period of neutropenia. For baseline infections, complete response and partial response were considered favourable clinical outcomes. A partial response was defined as clinically meaningful improvement in attributable symptoms and signs, as well as in attributable abnormalities detected by radiography, bronchoscopy, endoscopy or other procedures. Unfavorable responses included stable disease and failure. There were 1095 patients included in the primary Modified Intention-To-Treat (MITT) efficacy analysis of overall favourable response.

This trial was designed to establish noninferiority of CANCIDAS® to AmBisome§. The observed overall therapeutic success rates for CANCIDAS® and AmBisome§ were 34.2% and 33.6%, respectively, with an estimated difference (95.2% CI) of 0.2% (-5.6%, 6.0%). Results are summarized in Table14. The categories presented in Table 13 are not mutually exclusive. The therapeutic equivalence had no apparent relationship to the use of pre study prophylaxis or baseline risk factors.

CANCIDAS® had higher favorable response rates than AmBisome§ for patients with a baseline fungal infection (14/27 [51.9%]) and 7/27 [25.9%], respectively); however the number of patients with baseline infections was small in both groups. Response rates for CANCIDAS® and AmBisome§ for baseline infections caused by *Aspergillus* species were respectively, 41.7% (5/12) and 8.3% (1/12), and by *Candida* species were 66.7% (8/12) and 41.7% (5/12). Similarly, the proportion of patients not prematurely discontinued from study therapy due to toxicity or lack of efficacy was higher in the CANCIDAS® group (89.7%) compared with the AmBisome§ group (85.5%). The proportion of patients who discontinued due to a drug-related clinical or drug-related laboratory abnormality was lower among patients treated with CANCIDAS® (4.9%) than

among patients treated with AmBisome§ (8.2%). Similar proportions of patients in each group were discontinued due to lack of efficacy (5.4% vs 6.3%). Also absence of breakthrough infections (94.8% vs 95.5%), resolution of fever for 48 hours during neutropenia (41.2% vs 41.4%), and survival to 7-day post-treatment (92.6% vs 89.2%) had similar incidences in both groups. Distribution of probable or proven breakthrough infections is shown in Table 15.

TABLE 14
Favorable Response Rates in Febrile Neutropenic Patients

Endpoint	CANCIDAS® (N=556)	AmBisome§ (N=539)
	n/N** (%)	n/N (%)
Favorable response (overall)*	190/556 (34.2)	181/539 (33.6)
Successful treatment of baseline infections	14/27 (51.9)	7/27 (25.9)
Absence of breakthrough fungal infection	527/556(94.8)	515/539 (95.5)
Survival to 7-day follow-up	515/556 (92.6)	481/539 (89.2)
Study drug not prematurely discontinued due to drug-related toxicity or lack of efficacy	499/556 (89.7)	461/539 (85.5)
Resolution of fever for 48 hours during neutropenia	229/556 (41.2)	223/539 (41.4)

* The difference (95.2% CI) in the estimated favourable overall response was: 0.2% (-5.6, 6.0);
** Number of patients with favourable response/total number of MITT patients.

TABLE 15
Distribution of Probable or Proven Breakthrough Infections (MITT Population)

Breakthrough Invasive Fungal Infection*	CANCIDAS® (N=556)**	AmBisome§ (N=539)**
	Probable/Proven	Probable/Proven
Aspergillus species	10	9
Basidiomycetes	1	0
Candida species	16	15
Fusarium	1	0
Mould (NOS)	0	1
Zygomycetes	2	0

* Invasive fungal Infections were defined according to modified criteria of the European Organization for Research and Treatment of the Cancer-Mycosis Study Group,
** in the CANCIDAS® group there were 30 breakthrough infections in 29 patients and in the AmBisome§ group 25 breakthrough infections in 24 patients.

Invasive Candidiasis

Two hundred thirty-nine patients were enrolled in an initial study to compare CANCIDAS® and amphotericin B for the treatment of invasive candidiasis. The most frequent diagnoses were bloodstream infections (candidemia) (83%) and *Candida* peritonitis (10%). CANCIDAS® 50 mg once daily was administered following a 70 mg loading dose, while amphotericin B was administered at 0.6 to 0.7 mg/kg/day to non-neutropenic patients or 0.7 to 1.0 mg/kg/day to neutropenic patients. A favorable response required both symptom resolution and microbiological clearance of the *Candida* infection. Two hundred twenty-four patients were included in the primary efficacy analysis of response at the end of IV study therapy; favorable response rates for the treatment of invasive candidiasis were comparable for CANCIDAS® and amphotericin B. One hundred eighty-five patients who received at least 5 days of IV study therapy were included in a predefined efficacy analysis to support the primary analysis; in this

analysis, CANCIDAS® was statistically superior to amphotericin B at the end of IV study therapy. Among patients with candidemia, CANCIDAS® was comparable to amphotericin B at the end of IV study therapy in both the primary efficacy analysis and in the predefined efficacy analysis to support the primary analysis.

Favorable response rates at the end of IV study therapy are shown in Table 16.

TABLE 16
Favorable Response Rates to IV Study Therapy Among Patients with Invasive Candidiasis and Candidemia

	CANCIDAS® 50 mg* % (n/m) [95% CI]**	**Amphotericin B 0.6-1.0 mg/kg % (n/m) [95% CI]**	**Difference (%) After Adjusting for Strata**
ALL PATIENTS WITH INVASIVE CANDIDIASIS			
Primary analysis***	73.4% (80/109) [65.1, 81.7]	61.7% (71/115) [52.8, 70.7]	12.7% [-0.7, 26.0]††
Supporting analysis†	80.7% (71/88) [72.4, 89.0]	64.9% (63/97) [55.4, 74.5]	15.4% [1.1, 29.7]††
PATIENTS WITH CANDIDEMIA			
Primary analysis	71.7% (66/92) [62.5, 81.0]	62.8% (59/94) [52.9, 72.6]	10.0% [-4.5, 24.5]†††
Supporting analysis	80.3% (57/71) [71.0, 89.6]	64.6% (51/79) [53.9, 75.2]	15.2% [-0.6, 31.0]]†††

* Patients received CANCIDAS® 70 mg on Day 1, then 50 mg daily for the remainder of their treatment.
** Number of patients with favorable response at the end of IV study therapy/number of patients included in analysis
*** The primary analysis population consisted of patients who received at least one dose of therapy and had a documented diagnosis of invasive candidiasis.
† The supporting analysis population consisted of all patients who received at least 5 days of therapy, had a documented diagnosis of invasive candidiasis, had an end-of-therapy evaluation, and did not commit any protocol violations that interfered with the assessment of efficacy.
†† 95.6% confidence interval.
††† 95% confidence interval.

In a second 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 CANCIDAS® 150 mg/day. The diagnostic criteria, efficacy time points, and efficacy endpoints used in this study 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. A significant improvement in efficacy with the 150-mg daily dose was not seen when compared to the 50-mg dose.

Esophageal Candidiasis (and information on oropharyngeal candidiasis)
A Phase III, randomized, double-blind, controlled, non-inferiority, clinical trial and two small, comparative dose-ranging studies were conducted to evaluate the safety and efficacy of CANCIDAS® for the treatment of esophageal candidiasis. The Phase III clinical trial compared CANCIDAS® to intravenous fluconazole and the two dose-ranging studies compared different doses of CANCIDAS® to amphotericin B. In all three studies, patients were required to have symptoms and microbiological documentation of esophageal candidiasis. Most of the patients randomized in these studies had advanced AIDS (with CD4 counts < 50 cells/mm^3). *Candida* isolates were obtained from esophageal biopsies or brushes in 166 of the 177 patients enrolled in the Phase III clinical trial. One hundred twenty infections were due to *C. albicans* alone; two to *C. tropicalis* alone and the remainder were mixed infections with *C. albicans* and non-*C. albicans* species.

In the randomized, double-blind study comparing CANCIDAS® 50 mg/day versus IV fluconazole 200 mg/day for the treatment of esophageal candidiasis, patients were treated for an average of 9 days (range 7 to 21 days). A favourable overall response required both complete resolution of symptoms and significant endoscopic improvement 5 to 7 days following discontinuation of study therapy. 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. As shown in Table 17 the proportion of patients with a favourable overall response with CANCIDAS® was comparable to that seen with fluconazole (81.5% and 85.1%, respectively). 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 (85.2% and 86.2% for CANCIDAS® and fluconazole, respectively) was comparable.

TABLE 17
Favorable Response Rates for Patients with Esophageal Candidiasis (MITT Analysis)

	CANCIDAS® 50 mg n (%)*	**Fluconazole 200 mg n (%)***	**Observed Difference: % (95% Cl)****
Day 5-7 post-treatment	66/81 (81.5%)	80/94 (85.1%)	-3.6% (-14.7, 7.5)

* Number of patients with favorable response/number of patients with data at this time point.
** Calculated as CANCIDAS®-fluconazole.

The esophageal candidiasis relapse rates (Table 18) 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 18
Relapse Rates for Patients with Esophageal Candidiasis (MITT Analysis)

	CANCIDAS® 50 mg n (%)*	Fluconazole 200 mg n (%)*	Observed 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)

* Number of patients with favorable response/number of patients with data at this time point.
** Calculated as CANCIDAS®-fluconazole.

The results from the two dose-ranging studies corroborate the efficacy of CANCIDAS® for the treatment of esophageal candidiasis that was demonstrated in a Phase III study.

Oropharyngeal Candidiasis

Seventy percent (122) of the patients enrolled in the Phase III clinical study also had oropharyngeal candidiasis. A favorable response was defined as complete resolution of all symptoms of oropharyngeal candidiasis and all visible oropharyngeal lesions. The proportion of patients with favorable response was 71.4% for the CANCIDAS® group and 83.3% for the fluconazole group (Table 19) The relapse rates at Day 14 and 28 post-treatment (Table 20) were statistically significantly greater in the CANCIDAS® group compared with the fluconazole group at both dates.

TABLE 19
Oropharyngeal Candidiasis Response Rates in Patients with Oropharyngeal and Esophageal Candidiasis at Baseline (MITT Analysis)

Visit	CANCIDAS® 50 mg n (%)*	Fluconazole 200 mg n (%)*	Observed Difference: % (95% CI)**
Day 5-7 post-treatment	40/56 (71.4%)	55/66 (83.3%)	-11.9 (-26.8, 3.0)

* Number of patients with favorable response/number of patients with data at this time point.
** Calculated as CANCIDAS®-fluconazole.

TABLE 20
Oropharyngeal Candidiasis Relapse Rates in Patients with Oropharyngeal and Esophageal Candidiasis at Baseline (MITT Analysis)

Visit	CANCIDAS® 50 mg n (%)*	Fluconazole 200 mg n (%)*	Observed 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)

* Number of patients with favorable response/number of patients with data at this time point.
** Calculated as CANCIDAS®-fluconazole.

Invasive Aspergillosis

Patients between the ages of 18 and 80 with invasive aspergillosis were enrolled in an open-label, noncomparative study (n=69) 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 tomographic 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.[1] 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 (i.e. complete or partial response). For those patients who received > 7 days of therapy with CANCIDAS®, 50% (26/52) had a favourable response. The favourable 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.

Pediatric Patients

The safety and efficacy of CANCIDAS® was 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

[1] Denning DW, Lee JY, Hostetler JS, et al. NIAID Mycoses Study Group multicenter trial of oral itraconazole therapy for invasive aspergillosis. Am J Med 1994; 97:135-44.

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 TRIALS, Adult Patients, Empirical Therapy in febrile, neutropenic patients). 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.

Favourable overall response rates of pediatric patients with persistent fever and neutropenia are presented in Table 21.

TABLE 21
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 invasive candidiasis, 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 TRIALS, Adult Patients, Invasive Candidiasis, Esophageal Candidiasis (and information on oropharyngeal candidiasis, Oropharyngeal Candidiasis, and Invasive Aspergillosis). 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 MITT analysis. Of these 48 patients, 37 had invasive candidiasis, 10 had invasive aspergillosis, and 1 patient had esophageal candidiasis. The favorable response rate, by indication, at the end of caspofungin therapy was as follows in the MITT analysis: 81% (30/37) in invasive candidiasis, 50% (5/10) in invasive aspergillosis, and 100% (1/1) in esophageal candidiasis.

DETAILED PHARMACOLOGY

Pharmacokinetics

Absorption
Absorption is not relevant since caspofungin acetate is administered intravenously.

Distribution
Plasma concentrations of caspofungin decline in a polyphasic manner following single 1-hour IV infusions. A short α-phase occurs immediately post-infusion, 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 post-dose during which the plasma concentration decreases by an order of magnitude. An

additional, longer half-life phase, γ-phase, also occurs with a half-life of 27 hours. 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 [^{3}H] label was found in tissues 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. At later time points (≥ 5 days post-dose), there is a low level (≤ 7 pmol/mg protein, or ≤ 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. 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.

Elimination
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. Approximately 75% of the radioactivity was recovered: 41% in urine and 34% in feces. Plasma concentrations of radioactivity and of caspofungin were similar during the first 24 to 48 hours post-dose; thereafter drug levels fell more rapidly. In plasma, caspofungin concentrations fell below the limit of quantitation after 6 to 8 days post-dose, while radiolabel fell below the limit of quantitation at 22.3 weeks post-dose. 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; 2.5 μL/s*).

Special Populations and Conditions

Pediatrics
CANCIDAS® has been studied in five prospective studies involving pediatric patients under 18 years of age, including three pediatric pharmacokinetic studies (see INDICATIONS AND CLINICAL USE, Pediatrics (≤ 17 years of age)).

In adolescents (ages 12 to 17 years) receiving caspofungin at 50 mg/m^2 daily (maximum 70 mg daily), the caspofungin plasma $AUC_{0\text{-}24hr}$ was generally comparable to that seen in adults receiving caspofungin at 50 mg daily. All adolescents received doses > 50 mg daily, and, in fact, 6 of 8 received the maximum dose of 70 mg/day. The caspofungin plasma concentrations in these adolescents were reduced relative to adults receiving 70 mg daily, the dose most often administered to adolescents.

*International units

In children (ages 2 to 11 years) receiving caspofungin at 50 mg/m^2 daily (maximum 70 mg daily), the caspofungin plasma $AUC_{0\text{-}24hr}$ after multiple doses was comparable to that seen in adults receiving caspofungin at 50 mg/day. On the first day of administration, $AUC_{0\text{-}24hr}$ was somewhat higher in children than adults for these comparisons (37% increase for the 50 mg/m^2/day to 50 mg/day comparison). However, it should be recognized that the AUC values in these children on Day 1 were still less than those seen in adults at steady-state conditions.

In young children and toddlers (ages 3 to 23 months) receiving caspofungin at 50 mg/m^2 daily (maximum 70 mg daily), the caspofungin plasma $AUC_{0\text{-}24hr}$ after multiple doses was comparable to that seen in adults receiving caspofungin at 50 mg daily. As in the older children, these young children who received 50 mg/m^2 daily had slightly higher $AUC_{0\text{-}24hr}$ values on Day 1 relative to adults receiving the standard 50 mg daily dose. The caspofungin pharmacokinetic results from the young children (3 to 23 months of age) that received 50 mg/m^2 caspofungin daily were similar to the pharmacokinetic results from older children (2 to 11 years of age) that received the same dosing regimen.

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 20%) relative to men. No dosage adjustment is necessary based on gender.

Race
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.

Hepatic Insufficiency
Plasma concentrations of caspofungin after a single 70 mg dose (n=16) in adult patients with mild hepatic insufficiency (Child-Pugh score 5 to 6) were increased by approximately 55% compared to healthy historical control subjects. In a 14-day multiple-dose study (n=8) (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%) 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% 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, Patients with Hepatic Insufficiency). 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.

Renal Insufficiency
In a clinical study (n=36) of single 70 mg doses, caspofungin pharmacokinetics were similar in healthy adult volunteers with mild renal insufficiency (creatinine clearance 50 to 80 mL/min; 0.83 to 1.33 mL/s*) and control subjects. After single-dose administration, caspofungin AUC plasma concentration increased by 30 to 49% in patients with moderate (creatinine clearance

31 to 49 mL/min; 0.52 to 0.82 mL/s*), advanced (creatinine clearance 5 to 30 mL/min; 0.08 to 0.50 mL/s*), and end-stage (creatinine clearance < 10 mL/min [< 0.17 mL/s*] and dialysis dependent) renal insufficiency. However, in adult patients with invasive candidiasis (n=75) or invasive aspergillosis (n=69) 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.

MICROBIOLOGY

Activity *in vitro*

Standardized susceptibility testing methods for β (1,3)-D-glucan synthesis inhibitors have not been established, and results of susceptibility studies do not correlate with clinical outcome. Caspofungin has *in vitro* activity against *Aspergillus* species (including *Aspergillus fumigatus, Aspergillus flavus, and Aspergillus terreus,*) and *Candida* species (including *Candida albicans, Candida glabrata, Candida guilliermondii, Candida krusei, Candida parapsilosis,* and *Candida tropicalis)*. Susceptibility testing was performed according to the Clinical and Laboratory Standards Institute (CLSI, formerly known as the National Committee for Clinical Laboratory Standards [NCCLS] method M38-A2 (for *Aspergillus* species) and method M27-A3 (for *Candida* species).

Activity *in vivo*

Caspofungin, administered parenterally to immune-competent and immune-suppressed animals with disseminated infections of *Aspergillus* and *Candida* for which the endpoints were prolonged survival of infected animals (*Aspergillus* and *Candida*) and clearance of fungi from target organs (*Candida*). Caspofungin was also active in immunodeficient animals after disseminated infection with *C. glabrata, C. krusei, C. lusitaniae, C. parapsilosis, or C. tropicalis* in which the endpoint was clearance of *Candida* from target organs. In a lethal, rat pulmonary-infection model with *A. fumigatus*, caspofungin was highly active in the prevention and treatment of pulmonary aspergillosis.

Drug Resistance

A caspofungin MIC of ≤ 2 μg/mL ("Susceptible" per Table 13) using the CLSI M27-A3 method indicates that the *Candida* isolate is likely to be inhibited if caspofungin therapeutic concentrations are achieved. Breakthrough infections with *Candida* isolates requiring caspofungin concentrations > 2 μg/mL for growth inhibition have developed in a mouse model of *C. albicans* infection. **Isolates** of *Candida* with reduced susceptibility to caspofungin have been identified in a small number of patients during treatment (MICs for caspofungin > 2 μg/mL using standardized MIC testing techniques approved by the CLSI). Some of these isolates had mutations in the FKS1/FKS2 gene. Although the incidence is rare, these cases have been routinely associated with poor clinical outcomes.

In vitro drug resistance development to caspofungin in *Aspergillus* species has been studied. In clinical experience, drug resistance in patients with invasive aspergillosis has been observed.

*International units

The mechanism of resistance has not been established. Cases of drug resistance by various clinical isolates of *Candida* and *Aspergillus* species have been reported. Resistance development to caspofungin by *Candida* species occurs very rarely in the laboratory. Although increased MIC values could not be induced in *Candida* after serial passage in culture media containing caspofungin, prolonged exposure in a mouse model at subtherapeutic doses (approximately 1% or less of the human mg equivalent dose) suggests that there is a potential for resistance to develop.

Cross-resistance
Caspofungin acetate is active against strains of *Candida* with intrinsic or acquired resistance to fluconazole, amphotericin B, or flucytosine consistent with their different mechanisms of action. There are no data regarding the cross-resistance of caspofungin and other antifungal agents in treatment against *Aspergillus* species.

Drug Interactions
Studies *in vitro* and *in vivo* of caspofungin acetate, in combination with amphotericin B, demonstrate no antagonism of antifungal activity against *A. fumigatus*.

TOXICOLOGY

Animal Toxicology

Acute Toxicity
The approximate intravenous lethal dose $_{50}$ (LD_{50}) for female (male) mice and rats was calculated as 19 (27) and 38 mg/kg, respectively.

Chronic Toxicity
Several treatment-related changes were noted in intravenous toxicity studies in rats and Rhesus monkeys. In these studies, signs of histamine release were observed in rats, serum transaminase levels were increased in monkeys, and injection-site irritation was seen in both species.

In 5- and 14-week intravenous toxicity studies in rats, 5 mg/kg/day produced signs of histamine release consisting of hyperemia and swelling of the extremities, sluggish movement or ataxia, and recumbency. These signs occurred only during the first 7 to 9 days of dosing presumably due to endogenous histamine depletion. Overall, in the rat studies, 2 mg/kg/day was established as the no-effect level for histamine release. No signs of histamine release were reported in 5-, 14-, and 27-week intravenous dosing studies in monkeys. In ancillary pharmacology studies, a 20-minute infusion at 8 mg/kg produced no adverse effects in monkeys; however, bolus injections of 5 or 8 mg/kg did produce signs of histamine release. Similar signs of histamine release that were reversed upon injection of cyproheptadine were produced with structural analogs of caspofungin in monkeys.

In 5-, 14-, and 27-week intravenous toxicity studies in monkeys, ALT and/or AST levels were increased slightly to moderately, but these levels returned to baseline or remained slightly elevated over the course of the studies. The increases in serum transaminase values did not always correlate with microscopic evidence of hepatic damage (subcapsular necrosis). However, in a 5-week intravenous toxicity study in monkeys, several animals in the mid- and high-dose groups had correlating microscopic subscapular necrosis.

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.

During the 5-, 14-, and 27-week intravenous toxicity studies in rats and monkeys, clinical and histopathological signs of injection-site irritation were observed. Concentration-dependent injection-site irritation was minimized by pre- and post-dose flushing of catheter lines. Overall, the no-effect dosage level for irritation at the injection site in rats was 1.8 mg/kg/day (0.18 mg/mL), and in monkeys it was 3 mg/kg/day (0.25 mg/mL) with effective pre- and post-dose flushing of catheter lines.

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

Mutagenesis
Caspofungin acetate was evaluated in the following series of *in vitro* assays and found to be neither mutagenic nor genotoxic: bacterial (Ames) and mammalian cell (V79 Chinese hamster lung fibroblasts) mutagenesis assays, the alkaline elution/rat hepatocyte DNA strand break test, and the chromosomal aberration assay in Chinese hamster ovary cells. Additionally, in the *in vivo* mouse bone marrow chromosomal test, caspofungin acetate was not genotoxic at doses up to 12.5 mg/kg, administered intravenously.

Reproduction and Teratology
Female rats administered 0.5, 2, and 5 mg/kg/day of caspofungin acetate IV for 16 days prior to cohabitation, during cohabitation, and through gestation Day 7 showed no drug-related effects on mating performance, fecundity, fertility, or embryonic survival. Male rats treated intravenously with 0.5, 2, and 5 mg/kg/day (maximum dosage tested) for 28 days prior to mating showed no effect on fertility.

In rats, caspofungin caused decreases in fetal body weights and an increase in the incidence of incomplete ossification of the skull and torso at a maternally toxic dose of 5 mg/kg/day, which resulted in a plasma exposure approximately 1.5 times the plasma exposure seen in humans administered 70 mg. In addition, at this same maternally toxic dose, there was an increase in the incidence of cervical rib in rats. There were no developmental effects at a dose of 2 mg/kg/day.

In rabbits, there were no treatment-related external, visceral, or skeletal fetal morphological findings in an IV toxicity study where caspofungin acetate was administered to pregnant rabbits at doses of 1, 3, and 6 mg/kg/day on gestation Days 7 through 20. Therefore, the no-effect level for developmental toxicity is > 6 mg/kg/day. The no-effect level for maternal toxicity (based on minimal decreases in average maternal body weight gain and food consumption) was 3 mg/kg/day. Plasma exposures of approximately 1.5 times the human plasma exposure occurred in pregnant rabbits when administered caspofungin 5 mg/kg/day. Caspofungin has been shown to cross the placental barrier in animal studies.

In two rat and one rabbit reproductive toxicity studies, incidental findings included slight increases in the percent of peri-implantation and post-implantation loss relative to concurrent controls but within the historical control range. These observations were considered unrelated to treatment.

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PART III: CONSUMER INFORMATION

CANCIDAS®

caspofungin for injection
(as caspofungin acetate)

This leaflet is part III of a three-part "Product Monograph" published when CANCIDAS® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you or your child everything about CANCIDAS®. Contact your doctor or pharmacist if you or your child have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Your doctor has prescribed CANCIDAS® to treat one of several types of fungal infections described below.

- A serious fungal infection called invasive candidiasis. The infection is caused by fungal (yeast) cells called *Candida*. These yeast cells are normally found in the digestive tract, and do not cause an infection unless they enter the bloodstream (in which case the infection is referred to as candidemia) or other tissues or organs, such as the lining of the abdomen (peritonitis), the kidneys, the liver, bones, muscles, joints, spleen, or eyes. Persons at high risk for invasive candidiasis include surgical patients and those whose immune systems are deficient.

- Fungal infections of the mouth, back of the throat, and the food tube connecting the mouth to the stomach. These infections are called oropharyngeal candidiasis (mouth and back of the throat) or esophageal (food tube) candidiasis. The infection is also caused by *Candida*. Healthy individuals usually have *Candida* in their mouth and throat without any ill effects. An infection occurs when the body's resistance to disease is lowered.

    - A serious fungal infection called invasive aspergillosis. Invasive aspergillosis is a serious infection of the nose, nasal sinuses, and lungs. This infection may spread to other parts of the body. This kind of infection is caused by a number of common fungi found in the environment called *Aspergillus*. Most *Aspergillus* fungal infections begin in the respiratory system (in the nose, sinuses, or lungs) because the spores of the fungus are found in the air we breathe every day. In most healthy individuals, the natural ability to fight disease destroys the spores and removes them from the body. Some medical conditions lower the body's resistance to diseases. Also, certain medications prescribed for patients who are organ or bone marrow recipients lower the body's resistance to diseases. These are the patients who are most likely to develop these infections.

Also, your doctor may suspect that you have a fungal infection in the following situation, and prescribe CANCIDAS® to treat it. Chemotherapy or other medical treatments or conditions can lower the body's resistance to disease by lowering counts of certain white blood cells. If you have persistent fever following chemotherapy or under other conditions as noted above, and your fever is not reduced by treatment with an antibiotic, you may have a fungal infection.

What it does:
CANCIDAS® is an antifungal drug that interferes with the production of a component (glucan polysaccharide) of the fungal cell wall that is necessary if the fungus is to continue living and growing. Fungal cells exposed to CANCIDAS® have incomplete or defective cell walls, making them fragile and unable to grow.

When it should not be used:

Who should not receive CANCIDAS®?
CANCIDAS® should not be administered to you if you are allergic to any of its components (see "What the important nonmedicinal ingredients are").

Use in children and adolescents:
CANCIDAS® has been approved for use in children > 12 months of age and adolescents for all the infection types described above. The dose used in pediatric patients may differ from the dose used in adult patients.

What the medicinal ingredient is:
Caspofungin acetate

What the important nonmedicinal ingredients are:
Glacial acetic acid
Mannitol
Sodium hydroxide
Sucrose

This is a complete listing of all nonmedicinal ingredients.

What dosage forms it comes in:
Powder for injection, 50, 70 mg vials/cartons

WARNINGS AND PRECAUTIONS

Serious warnings and precautions:
The use of CANCIDAS® and cyclosporine at the same time is not recommended.

Use in pregnancy and breast-feeding:

CANCIDAS® has not been studied in pregnant women. CANCIDAS® should be used in pregnancy only if the doctor determines that the potential benefit justifies the potential risk to the fetus.

Women receiving CANCIDAS® should not breast-feed.

Use in patients with Hepatic Insufficiency:
Some patients with liver problems may require a dosage adjustment. Be sure to tell you doctor if you have had or now have liver problems.

BEFORE you use CANCIDAS® talk to your doctor or pharmacist if:

- You have a history of allergic skin reactions (See "Side Effects and What to Do About Them")
- You are taking cyclosporine
- In addition, you should always tell your doctor about all other medications that you are taking or plan to take, including those obtained without a prescription. It is particularly important for your doctor to know if you are taking certain anti-HIV drugs (including efavirenz or nevirapine), the antiseizure (epilepsy) medications phenytoin and carbamazepine, the steroid dexamethasone, the antibiotic rifampin, and the immunosuppressant tacrolimus.
- You have liver problems
- You are pregnant or planning to become pregnant
- You are breast feeding or planning to breastfeed
- You are allergic to any component of CANCIDAS®

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with CANCIDAS® include

- Carbamazepine
- Cyclosporine
- Dexamethasone
- Efavirenz
- Nevirapine
- Phenytoin
- Rifampin
- Tacrolimus

PROPER USE OF THIS MEDICATION

Usual adult dose:
The treatment schedule and dosage will be set by your doctor, who will monitor your response and condition. CANCIDAS® should be administered once daily by slow intravenous infusion of approximately 1 hour.

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

If you are treated for fungal infections of the mouth, back of the throat, and the food tube connecting the mouth to the stomach, 50 mg should be administered on Day 1 and daily thereafter.

Overdose:

If you are concerned that you may have been given too much CANCIDAS®, contact your doctor, hospital emergency department or regional poison control centre, even if there are no symptoms

Missed dose:

If you are concerned that you may have missed a dose, contact your doctor immediately.

No dosage adjustment is necessary for the elderly.

No dosage adjustment is necessary for patients with reduced kidney function.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Anemia (low red blood cells with symptoms such as weakness, tiredness, shortness of breath, pale skin)		✓	
	Liver problems with symptoms such as yellowing of the skin and eyes, abdominal pain, nausea, vomiting, pale stool.		✓	
	Swollen veins (phlebitis/thrombophlebitis)	✓		
Uncommon	Serious allergic reaction and symptoms such as severe rash, itching, swelling of hands and feet, swelling of face and lips, trouble breathing			✓

Any medicine may have unintended or undesirable effects, so-called side effects.

The most common medication-related undesirable effects in adults are fever and vein irritations at the infusion site (itching, redness, swelling, or clotting).

Other reported medication-related undesirable effects in adults include: headache, pain, bone pain, chills, rapid heartbeats, sweating, nausea, diarrhea, vomiting, rash, skin redness, itching, trouble breathing, swelling of the hands, ankles, or feet, impaired liver function, and alterations in some laboratory blood tests.

The most common medication-related undesirable effects in children and adolescents are fever, rash, and headache. Other reported medication-related undesirable effects in children and adolescents include: pain at the catheter site, chills, rapid heartbeat, flushing, itching, low blood pressure and alterations in some laboratory blood tests.

Life-threatening allergic reactions have been reported rarely during administration of CANCIDAS® and symptoms may include swelling of the face, lips and throat, difficulty in breathing, rash, itching, or sensation of warmth. If any

combination of these symptoms occurs contact your doctor immediately.
Additionally, while the medicine has been on the market, the following have also been reported:

- Severe, life-threatening skin conditions such as toxic epidermal necrolysis and Stevens- Johnson syndrome.

Contact your doctor immediately if you develop serious skin adverse reactions such as a severe rash, blisters, hives, large areas of peeling skin, mucous membrane sores or extensive sores in the mouth, throat and skin, often with accompanying fever, fatigue, flu-like symptoms and skin infection.

Other side effects may also occur rarely; and, as with any prescription medication, some side effects may be serious. Ask your doctor or pharmacist for more information. Tell your doctor or pharmacist promptly about these or any other unusual symptoms.

This is not a complete list of side effects. For any unexpected effects while taking CANCIDAS® contact your doctor or pharmacist.

HOW TO STORE IT

Unopened vials of CANCIDAS® should be stored *refrigerated* at 2°C to 8°C.

Reconstituted CANCIDAS® should be used immediately because it does not contain any preservatives to prevent bacterial contamination. Only a trained healthcare professional who has access to the complete directions provided with each vial can properly prepare this medication for use.

REPORTING SIDE EFFECTS

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at www.healthcanada.gc.ca/medeffect
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax toll-free to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 1908C
    Ottawa, ON K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about CANCIDAS®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website or Merck Canada website www.merck.ca or by calling Merck Canada at 1-800-567-2594.

This leaflet was prepared by Merck Canada Inc.

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