MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

9344301

INTRAVENOUS INFUSION (not for IV Bolus Injection)

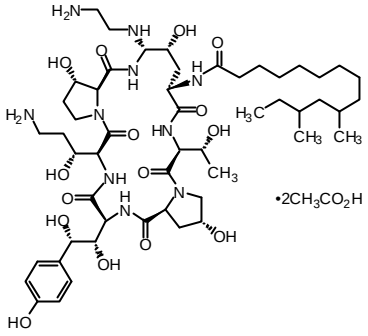
CANCIDAS®

(caspofungin acetate) FOR INJECTION

DESCRIPTION

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

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



CLINICAL PHARMACOLOGY

Pharmacokinetics

Distribution

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

Metabolism

Caspofungin is slowly metabolized by hydrolysis and N-acetylation. Caspofungin also undergoes spontaneous chemical degradation to an open-ring peptide compound, L-747969. At later time points (5 to 20 days postdose), there is a low level (3 to 7 picomoles/mg protein, or 0.6 to 1.3% of administered dose) of covalent binding of radiolabel in plasma following single-dose administration of [^{3}H] caspofungin acetate, which may be due to two reactive intermediates formed during the chemical degradation of caspofungin to L-747969. Additional metabolism involves hydrolysis into constitutive amino acids and their degradates, including dihydroxyhomotyrosine and N-acetyl-dihydroxyhomotyrosine. These two tyrosine derivatives are found only in urine, suggesting rapid clearance of these derivatives by the kidneys.

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Excretion

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

Special Populations

Gender

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

Geriatric

Plasma concentrations of caspofungin in healthy older men and women (≥65 years of age) were increased slightly (approximately 28% AUC) compared to young healthy men after a single 70-mg dose of caspofungin. Age is not a significant determinant of caspofungin pharmacokinetics in patients with fungal infections. No dosage adjustment is necessary for the elderly (see PRECAUTIONS, *Geriatric Use*).

Race

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

Renal Insufficiency

In a clinical study of single 70-mg doses, caspofungin pharmacokinetics were similar in volunteers with mild renal insufficiency (creatinine clearance 50 to 80 mL/min) and control subjects. Moderate (creatinine clearance 31 to 49 mL/min), advanced (creatinine clearance 5 to 30 mL/min), and end-stage (creatinine clearance <10 mL/min and dialysis dependent) renal insufficiency moderately increased caspofungin plasma concentrations after single-dose administration (range: 30 to 49% for AUC). However, in patients with invasive aspergillosis who received multiple daily doses of CANCIDAS 50 mg, there was no significant effect of mild to advanced renal impairment on caspofungin trough concentrations. No dosage adjustment is necessary for patients with renal insufficiency. Caspofungin is not dialyzable, thus supplementary dosing is not required following hemodialysis.

Hepatic Insufficiency

Plasma concentrations of caspofungin after a single 70-mg dose in patients with mild hepatic insufficiency (Child-Pugh score 5 to 6) were increased by approximately 55% in AUC compared to healthy control subjects. In a 14-day multiple-dose study (70 mg on Day 1 followed by 50 mg daily thereafter), plasma concentrations in patients with mild hepatic insufficiency were increased modestly (19 to 25% in AUC) on Days 7 and 14 relative to healthy control subjects. No dosage adjustment is recommended for patients with mild hepatic insufficiency. Patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9) who received a single 70-mg dose of CANCIDAS had an average plasma caspofungin increase of 76% in AUC compared to control subjects. A dosage reduction is recommended for patients with moderate hepatic insufficiency (see DOSAGE AND ADMINISTRATION). There is no clinical experience in patients with severe hepatic insufficiency (Child-Pugh score >9).

Pediatric Patients

CANCIDAS has not been adequately studied in patients under 18 years of age.

MICROBIOLOGY

Mechanism of Action

Caspofungin acetate, the active ingredient of CANCIDAS, inhibits the synthesis of β (1,3)-D-glucan, an essential component of the cell wall of susceptible *Aspergillus* species and *Candida* species. β (1,3)-D-glucan is not present in mammalian cells. Caspofungin has shown activity against *Candida* species and in regions of active cell growth of the hyphae of *Aspergillus fumigatus*.

Activity in vitro

Caspofungin exhibits *in vitro* activity against *Aspergillus* species (*Aspergillus fumigatus*, *Aspergillus flavus*, and *Aspergillus terreus*) and *Candida* species (*Candida albicans, Candida glabrata,* and *Candida*

guilliermondii). Susceptibility testing was performed according to the National Committee for Clinical Laboratory Standards (NCCLS) method M38-A (for *Aspergillus* species) and M27-A (for *Candida* species). Standardized susceptibility testing methods for β (1,3)-D-glucan synthesis inhibitors have not been established for yeasts and filamentous fungi, and results of susceptibility studies do not correlate with clinical outcome.

Activity in vivo

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

Drug Resistance

A study in mice infected with *C. albicans* and treated with orally administered doses of caspofungin suggests that there is a potential for resistance development to occur. *In vitro* resistance development to caspofungin by *Aspergillus* species has not been studied. In limited clinical experience, drug resistance in patients with invasive aspergillosis has not been observed. The incidence of drug resistance by various clinical isolates of *Candida* and *Aspergillus* species is unknown.

Drug Interactions

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

CLINICAL STUDIES

Esophageal Candidiasis (and information on oropharyngeal candidiasis)

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

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

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

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

The proportion of patients with a favorable overall response for the primary endpoint was comparable for CANCIDAS and fluconazole as shown in the following table.

Favorable Response Rates for Patients with Esophageal Candidiasis

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

* calculated as CANCIDAS – fluconazole

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

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

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

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

* calculated as CANCIDAS – fluconazole

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

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

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

* calculated as CANCIDAS – fluconazole

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

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

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

* calculated as CANCIDAS – fluconazole

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

Invasive Aspergillosis

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

[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; 97:135-144.

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

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

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

INDICATIONS AND USAGE

CANCIDAS is indicated for the treatment of:

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

CONTRAINDICATIONS

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

WARNINGS

Concomitant use of CANCIDAS with cyclosporine is not recommended unless the potential benefit outweighs the potential risk to the patient. In one clinical study, 3 of 4 healthy subjects who received CANCIDAS 70 mg on Days 1 through 10, and also received two 3 mg/kg doses of cyclosporine 12 hours apart on Day 10, developed transient elevations of alanine transaminase (ALT) on Day 11 that were 2 to 3 times the upper limit of normal (ULN). In a separate panel of subjects in the same study, 2 of 8 who received CANCIDAS 35 mg daily for 3 days and cyclosporine (two 3 mg/kg doses administered 12 hours apart) on Day 1 had small increases in ALT (slightly above the ULN) on Day 2. In both groups, elevations in aspartate transaminase (AST) paralleled ALT elevations, but were of lesser magnitude (see ADVERSE REACTIONS). Hence, concomitant use of CANCIDAS with cyclosporine is not recommended until multiple-dose use in patients is studied.

PRECAUTIONS

General

The efficacy of a 70-mg dose regimen in patients with invasive aspergillosis who are not clinically responding to the 50-mg daily dose is not known. Limited safety data suggest that an increase in dose to 70 mg daily is well tolerated. For candidiasis, see CLINICAL STUDIES. The safety and efficacy of doses above 70 mg have not been adequately studied.

The safety information on treatment durations longer than 2 weeks is limited, however, available data suggest that CANCIDAS continues to be well tolerated with longer courses of therapy (74 patients received from 15 to 60 days of therapy; 14 patients received from 61 to 162 days of therapy).

Drug Interactions

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

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

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

In two 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 ADVERSE REACTIONS).

A drug-drug interaction study with rifampin in healthy volunteers has shown a 30% decrease in caspofungin trough concentrations. Patients on rifampin should receive 70 mg of CANCIDAS daily. In addition, results from regression analyses of patient pharmacokinetic data suggest that co-administration of other inducers of drug clearance (efavirenz, nevirapine, phenytoin, dexamethasone, or carbamazepine) with CANCIDAS may result in clinically meaningful reductions in caspofungin concentrations. It is not known which drug clearance mechanism involved in caspofungin disposition may be inducible**.** When CANCIDAS is co-administered with inducers of drug clearance, such as efavirenz, nevirapine, phenytoin, dexamethasone, or carbamazepine, use of a daily dose of 70 mg of CANCIDAS should be considered.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

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

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

Pregnancy

Pregnancy Category C. CANCIDAS 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 periimplantation 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. There are no adequate and well-controlled studies in pregnant women. CANCIDAS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

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

Patients with Hepatic Insufficiency

Patients with mild hepatic insufficiency (Child-Pugh score 5 to 6) do not need a dosage adjustment. For ~~patients with esophageal and/or~~ oropharyngeal candidiasis and moderate hepatic insufficiency (Child-Pugh

[2] Registered trademark of Fujisawa Healthcare, Inc.

score 7 to 9), CANCIDAS 35 mg daily is recommended. For patients with invasive aspergillosis and moderate hepatic insufficiency, after the initial 70-mg loading dose, CANCIDAS 35 mg daily is recommended. There is no clinical experience in patients with severe hepatic insufficiency (Child-Pugh score >9).

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of CANCIDAS did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Although the number of elderly patients was not large enough for a statistical analysis, no overall differences in safety or efficacy were observed between these and younger patients. Plasma concentrations of caspofungin in healthy older men and women (≥65 years of age) were increased slightly (approximately 28% in AUC) compared to young healthy men. No dose adjustment is recommended for the elderly; however, greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

General

Possible histamine-mediated symptoms have been reported including isolated reports of rash, facial swelling, pruritus, sensation of warmth, or bronchospasm. One case of anaphylaxis characterized by dyspnea, stridor, and worsening of rash during initial administration of CANCIDAS was reported.

Clinical Adverse Experiences

The overall safety of caspofungin was assessed in 631 individuals who received single or multiple doses of caspofungin acetate. There were 285 patients with esophageal and/or oropharyngeal candidiasis and 72 patients with invasive aspergillosis enrolled in phase II and phase III clinical studies. The remaining 274 individuals were enrolled in phase I studies. Most of the patients in the *Candida* studies had advanced AIDS (with low CD4 counts <50 mm^3). Many of these patients also had multiple opportunistic infections related to their HIV infection. 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.

Clinical adverse experiences with an incidence ≥2%, reported in patients treated with CANCIDAS in the noncomparative aspergillosis study are presented in Table 1.

TABLE 1
Drug-related Clinical Adverse Experiences in Patients with Invasive Aspergillosis (open-label, noncomparative study)*
Incidence ≥2% by Body System

	CANCIDAS 50 mg N=69 (percent)
Body as a Whole	
Fever	2.9
Peripheral Vascular System	
Infused vein complications	2.9
Digestive System	
Nausea	2.9
Vomiting	2.9
Skin & Skin Appendage	
Flushing	2.9

*Relationship to drug was 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.

Also reported infrequently in this patient population were pulmonary edema, ARDS, and radiographic infiltrates.

Laboratory abnormalities with an incidence ≥2%, reported in patients treated with CANCIDAS in the noncomparative aspergillosis study are presented in Table 2.

CANCIDAS®
(caspofungin acetate)

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TABLE 2
Drug-related Laboratory Abnormalities Reported Among Patients with Invasive Aspergillosis (open-label, noncomparative study)*
Incidence ≥2% by Laboratory Test Category

	CANCIDAS 50 mg N=69 (percent)
Blood Chemistry	
Serum alkaline phosphatase increased	2.9
Serum potassium decreased	2.9
Hematology	
Eosinophils increased	3.2
Urinalysis	
Urine protein increased	4.9
Urine RBCs increased	2.2

*Relationship to drug was 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.

Drug-related clinical adverse experiences occurring in ≥2% of patients with esophageal and/or oropharyngeal candidiasis are presented in Table 3.

TABLE 3
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 (percent)	Fluconazole IV 200 mg** N=94 (percent)	CANCIDAS 50 mg*** N=80 (percent)	CANCIDAS 70 mg*** N=65 (percent)	Amphotericin B 0.5 mg/kg*** N=89 (percent)
Body as a Whole					
Asthenia/fatigue	†	†	†	†	6.7
Chills	†	†	2.5	1.5	75.3
Edema/swelling	†	†	†	†	5.6
Edema, facial	†	†	†	3.1	†
Fever	3.6	1.1	21.3	26.2	69.7
Flu-like illness	†	†	†	3.1	†
Malaise	†	†	†	†	5.6
Pain	†	†	1.3	4.6	5.6
Pain, abdominal	3.6	2.1	2.5	†	9.0
Warm sensation	†	†	†	1.5	4.5
Peripheral Vascular System					
Infused vein complication	12.0	8.5	2.5	1.5	†
Phlebitis/thrombophlebitis	15.7	8.5	11.3	13.8	22.5
Cardiovascular System					
Tachycardia	†	†	1.3	†	4.5
Vasculitis	†	†	†	†	3.4
Digestive System					
Anorexia	†	†	1.3	†	3.4
Diarrhea	3.6	2.1	1.3	3.1	11.2
Gastritis	†	2.1	†	†	†
Nausea	6.0	6.4	2.5	3.1	21.3
Vomiting	1.2	3.2	1.3	3.1	13.5
Hemic & Lymphatic System					
Anemia	†	†	3.8	†	9.0
Metabolic/Nutritional/Immune					
Anaphylaxis	†	†	†	†	2.2
Musculoskeletal System					
Myalgia	1.2	†	†	3.1	2.2
Pain, back	†	†	†	†	2.2
Pain, musculoskeletal	†	†	1.3	†	4.5
Nervous System & Psychiatric					
Dizziness	†	2.1	†	1.5	1.1
Headache	6.0	1.1	11.3	7.7	19.1
Insomnia	1.2	†	†	†	2.2
Paresthesia	†	†	1.3	3.1	1.1
Tremor	†	†	†	†	7.9
Respiratory System					
Tachypnea	†	†	1.3	†	4.5
Skin & Skin Appendage					
Erythema	1.2	†	1.3	1.5	7.9
Induration	†	†	†	3.1	6.7
Pruritus	1.2	†	2.5	1.5	†
Rash	†	†	1.3	4.6	3.4
Sweating	†	†	1.3	†	3.4

*Relationship to drug was determined by the investigator to be possibly, probably or definitely drug-related.
** Derived from a Phase III comparator-controlled clinical study.
*** Derived from Phase II comparator-controlled clinical studies.
† Incidence 0.0%.

Laboratory abnormalities occurring in ≥2% of patients with esophageal and/or oropharyngeal candidiasis are presented in Table 4.

TABLE 4
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 (percent)	CANCIDAS 70 mg*** N=65 (percent)	Fluconazole IV 200 mg** N=94 (percent)	Amphotericin B 0.5 mg/kg*** N=89 (percent)
Blood Chemistry				
ALT increased	10.6	10.8	11.8	22.7
AST increased	13.0	10.8	12.9	22.7
Blood urea increased	†	†	1.2	10.3
Direct serum bilirubin increased	0.6	†	3.3	2.5
Serum albumin decreased	8.6	4.6	5.4	14.9
Serum alkaline phosphatase increased	10.5	7.7	11.8	19.3
Serum bicarbonate decreased	0.9	†	†	6.6
Serum calcium decreased	1.9	†	3.2	1.1
Serum creatinine increased	†	1.5	2.2	28.1
Serum potassium decreased	3.7	10.8	4.3	31.5
Serum potassium increased	0.6	†	2.2	1.1
Serum sodium decreased	1.9	1.5	3.2	1.1
Serum uric acid increased	0.6	†	†	3.4
Total serum bilirubin increased	†	†	3.2	4.5
Total serum protein decreased	3.1	†	3.2	3.4
Hematology				
Eosinophils increased	3.1	3.1	1.1	1.1
Hematocrit decreased	11.1	1.5	5.4	32.6
Hemoglobin decreased	12.3	3.1	5.4	37.1
Lymphocytes increased	†	1.6	2.2	†
Neutrophils decreased	1.9	3.1	3.2	1.1
Platelet count decreased	3.1	1.5	2.2	3.4
Prothrombin time increased	1.3	1.5	†	2.3
WBC count decreased	6.2	4.6	8.6	7.9
Urinalysis				
Urine blood increased	†	†	†	4.0
Urine casts increased	†	†	†	8.0
Urine pH increased	0.8	†	†	3.6
Urine protein increased	1.2	†	3.3	4.5
Urine RBCs increased	1.1	3.8	5.1	12.0
Urine WBCs increased	†	7.7	†	24.0

*Relationship to drug was determined by the investigator to be possibly, probably or definitely drug-related.
** Derived from Phase II and Phase III comparator-controlled clinical studies.
*** Derived from Phase II comparator-controlled clinical studies.
† Incidence 0.0%.

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

OVERDOSAGE

In clinical studies the highest dose was 100 mg, administered as a single dose to 5 patients. This dose was generally well tolerated. No overdosages have been reported. Caspofungin is not dialyzable. The minimum lethal dose of caspofungin in rats was 50 mg/kg, a dose which is equivalent to 10 times the recommended daily dose based on relative body surface area comparison.

ANIMAL PHARMACOLOGY AND TOXICOLOGY

In one 5-week study in monkeys at doses which produced exposures approximately 4 to 6 times those seen in patients treated with a 70-mg dose, scattered small foci of subcapsular necrosis were observed

microscopically in the livers of some animals (2/8 monkeys at 5 mg/kg and 4/8 monkeys at 8mg/kg); however, this histopathological finding was not seen in another study of 27 weeks duration at similar doses.

DOSAGE AND ADMINISTRATION

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

Esophageal Candidiasis

50 mg daily should be administered by slow IV infusion over approximately 1 hour. Because of the risk of relapse of oropharyngeal candidiasis in patients with HIV infections, suppressive oral therapy could be considered (see CLINICAL STUDIES). 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 IV 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 suggests that an increase in dose to 70 mg daily is well tolerated. The safety and efficacy of doses above 70 mg have not been adequately studied.

Hepatic Insufficiency

Patients with mild hepatic insufficiency (Child-Pugh score 5 to 6) do not need a dosage adjustment. For patients with esophageal and/or oropharyngeal candidiasis and moderate hepatic insufficiency (Child-Pugh score 7 to 9), CANCIDAS 35 mg daily is recommended. For patients with invasive aspergillosis and moderate hepatic insufficiency, after the initial 70-mg loading dose, CANCIDAS 35 mg daily is recommended. There is no clinical experience in patients with severe hepatic insufficiency (Child-Pugh score >9) (see CLINICAL PHARMACOLOGY, *Pharmacokinetics, Special Populations*).

Concomitant Medication with Inducers of Drug Clearance

Patients on rifampin should receive 70 mg of CANCIDAS daily. Patients on nevirapine, efavirenz, carbamazepine, dexamethasone, or phenytoin may require an increase in dose to 70 mg of CANCIDAS daily (see PRECAUTIONS, *Drug Interactions*).

Preparation of CANCIDAS for use:

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

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

1. Equilibrate the refrigerated vial of CANCIDAS to room temperature.
2. Aseptically add 10.5 mL of 0.9% Sodium Chloride Injection, Sterile Water for Injection, Bacteriostatic Water for Injection with methylparaben and propylparaben, or Bacteriostatic Water for Injection with 0.9% benzyl alcohol to the vial.[a] This reconstituted solution may be stored for up to one hour at ≤25°C (≤77°F).[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% Sodium Chloride Injection, or Lactated Ringer's Injection. This infusion solution must be used within 24 hours if stored at ≤25°C (≤77°F) or within 48 hours if stored refrigerated at 2 to 8°C (36 to 46°F). (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

1. Equilibrate the refrigerated vial of CANCIDAS to room temperature.
2. Aseptically add 10.5 mL of 0.9% Sodium Chloride Injection, Sterile Water for Injection, Bacteriostatic Water for Injection with methylparaben and propylparaben, or Bacteriostatic Water for Injection with 0.9% benzyl alcohol to the vial.[a] This reconstituted solution may be stored for up to one hour at ≤25°C (≤77°F).[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% Sodium Chloride Injection, or Lactated Ringer's Injection. This infusion solution must be used within 24 hours if stored at ≤25°C (≤77°F) or within 48 hours if stored refrigerated at 2 to 8°C (36 to 46°F). (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

Preparation of 70-mg Day 1 loading dose from two 50-mg vials for Invasive Aspergillosis

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 of 0.9%, 0.45%, or 0.225% Sodium Chloride Injection, or Lactated Ringer's Injection.

Preparation of 50-mg daily doses at reduced volume

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% Sodium Chloride Injection, or Lactated Ringer's Injection (see *Preparation of the daily 50-mg infusion*).

Preparation of a 35-mg daily dose for 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 or, if medically necessary, to 100 mL of 0.9%, 0.45%, or 0.225% Sodium Chloride Injection or Lactated Ringer's Injection.

Preparation notes:

a The white to off-white cake will dissolve completely. Mix gently until a clear solution is obtained.

b Visually inspect the reconstituted solution for particulate matter or discoloration during reconstitution and prior to infusion. Do not use if the solution is cloudy or has precipitated.

c CANCIDAS is formulated to provide the full labeled vial dose (70 mg or 50 mg) when 10 mL is withdrawn from the vial.

TABLE 5
CANCIDAS Concentrations

Dose	Reconstituted Solution Concentration	Infusion Volume	Infusion Solution Concentration
70-mg initial dose for IA	7.2 mg/mL	260 mL	0.28 mg/mL
50-mg daily dose	5.2 mg/mL	260 mL	0.20 mg/mL
70-mg initial dose for IA* (from two 50 mg vials)	5.2 mg/mL	264 mL	0.28 mg/mL
50-mg daily dose* (reduced volume)	5.2 mg/mL	110 mL	0.47 mg/mL
35-mg daily dose* (from one 50 mg vial) for Moderate Hepatic Insufficiency	5.2 mg/mL or 5.2 mg/mL	257 mL or 107 mL	0.14 mg/mL or 0.34 mg/mL

*See preceding text for these special situations.

HOW SUPPLIED

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

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

No. 3823 — CANCIDAS 70 mg is a white to off-white powder/cake for infusion in a vial with a yellow/orange aluminum band and a plastic cap.

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

Storage

Vials

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

Reconstituted Concentrate

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

Diluted Product

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

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