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WPC-CAN-IV-032002

WORLDWIDE PRODUCT CIRCULAR

CANCIDAS™ (caspofungin acetate) FOR INJECTION

MANDATORY SECTION

I. THERAPEUTIC CLASS

CANCIDAS* is a sterile, lyophilized product for intravenous infusion that contains a semi-synthetic 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.

II. INDICATIONS

CANCIDAS is indicated for the treatment of:

- Invasive Candidiasis, including candidemia, in neutropenic and non-neutropenic patients
- Esophageal Candidiasis
- Oropharyngeal Candidiasis
- Invasive Aspergillosis in patients who are refractory to or intolerant of other therapies

III. DOSAGE AND ADMINISTRATION

[For additional Dosage and Administration text see OPTIONAL section XIVA]

[To add the optional Transfer set preparation instructions, add OPTIONAL Section XIVb]

[For alternative text, see ALTERNATIVE Section XXIII.]

General Recommendations

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 and Oropharyngeal Candidiasis

Fifty (50) mg daily should be administered by slow intravenous infusion over approximately 1 hour.

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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. Although there is no information to demonstrate an increase in efficacy with higher doses, available safety data suggest that an increase in dose to 70 mg daily may be considered in patients without evidence of clinical response in whom CANCIDAS has been well tolerated.

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

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

When co-administering CANCIDAS with the metabolic inducers efavirenz, nevirapine, rifampin, dexamethasone, phenytoin, or carbamazepine, use of a daily dose of 70 mg of CANCIDAS should be considered.

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 score 7 to 9), CANCIDAS 35 mg daily is recommended. For patients with invasive candidiasis or 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 greater than 9).

Reconstitution of CANCIDAS

DO NOT USE ANY DILUENTS CONTAINING DEXTROSE (α -D-GLUCOSE), as CANCIDAS is not stable in diluents containing dextrose. DO NOT MIX OR CO-INFUSE CANCIDAS WITH ANY OTHER MEDICATIONS, as there are no data available on the compatibility of CANCIDAS with other intravenous substances, additives, or medications. Visually inspect the infusion solution for particulate matter or discoloration.

Step 1 Reconstitution of conventional vials

To reconstitute the powdered drug, bring the refrigerated conventional vial of CANCIDAS to room temperature and aseptically add 10.5 mL of either Sterile Water for Injection, Bacteriostatic Water for Injection with methylparaben and propylparaben, or Bacteriostatic Water for Injection with 0.9% benzyl alcohol. The concentrations of the reconstituted vials will be: 7 mg/mL (70 mg vial) or 5 mg/mL (50 mg vial).

The white to off-white compact powder will dissolve completely. Mix gently until a clear solution is obtained. Reconstituted solutions should be visually inspected for particulate matter or discoloration. This reconstituted solution may be stored for up to 24 hours at or below 25°C (77°F).

Step 2 Addition of Reconstituted CANCIDAS to patient infusion solution

Diluents for the final patient infusion solutions are: Sterile Saline for Injection, or Lactated Ringer's Solution. The standard patient infusion is prepared by aseptically adding the appropriate amount of reconstituted drug (as shown in the table below) to a 250 mL intravenous bag or bottle. Reduced volume infusions in 100 mL may be used, when medically necessary, for 50 mg or 35 mg daily doses. Do not use if the solution is cloudy or precipitated. This infusion solution must be used within 24 hours if stored at or below 25°C (77°F) or within 48 hours if stored refrigerated at 2 to 8°C (36 to 46°F). CANCIDAS should be administered by slow intravenous infusion over approximately 1 hour.

PREPARATION OF THE PATIENT INFUSION SOLUTIONS

DOSE*	Volume of reconstituted CANCIDAS for transfer to intravenous bag or bottle	Typical preparation (reconstituted CANCIDAS added to 250 mL) final concentration	Reduced volume infusion (reconstituted CANCIDAS added to 100 mL) final concentration
70 mg	10 mL	0.27 mg/mL	not recommended
70 mg (from two 50 mg vials)**	14 mL	0.27 mg/mL	not recommended
50 mg	10 mL	0.19 mg/mL	0.45 mg/mL
35 mg for moderate hepatic insufficiency (from one 50 mg vial)	7 mL	0.14 mg/mL	0.33 mg/mL

* 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

IV. CONTRAINDICATIONS

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

V. PRECAUTIONS

[For alternative text, see Alternative Section XXV.]

Concomitant use of CANCIDAS with cyclosporine is not recommended. Some healthy subjects who received two 3 mg/kg doses of cyclosporine with caspofungin showed transient increases in alanine transaminase (ALT) and aspartate transaminase (AST) of less than or equal to 3-fold the upper limit of normal (ULN) that resolved with discontinuation of the drugs. There was also an increase of approximately 35% in the area under the curve (AUC) of caspofungin when CANCIDAS and cyclosporine were co-administered; blood levels of cyclosporine remained unchanged.

VI. PREGNANCY

For additional animal toxicology text, add OPTIONAL Section XV Pregnancy]

[For alternative text with pregnancy category, see ALTERNATIVE Section XXIV.]

There is no clinical experience involving pregnant women. 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. In addition, at this same maternally toxic dose, there was an increase in the incidence of cervical rib in rats. Caspofungin has been shown to cross the placental barrier in animal studies.

CANCIDAS should not be used during pregnancy unless clearly necessary.

VII. NURSING MOTHERS

It is not known whether this drug is excreted in human milk; therefore, women receiving CANCIDAS should not breast-feed.

VIII. PEDIATRIC USE

Caspofungin acetate has not been studied in pediatric patients. Use in patients under 18 years of age is not recommended.

IX. USE IN THE ELDERLY

The plasma concentration of caspofungin in healthy older men and women (65 years of age or more) was increased slightly (approximately 28% in AUC) compared to young healthy males. In patients with invasive candidiasis, a similar modest effect of age was seen in older patients relative to younger patients. No dosage adjustment is necessary for elderly patients (65 years of age or more).

X. 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, rifampin, or the active metabolite of mycophenolate.

CANCIDAS reduced the 12-hour blood concentration (C_{12hr}) of tacrolimus (FK-506) by 26%. 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%. These AUC increases are probably due to reduced uptake of caspofungin by the liver. 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.

Results from two clinical drug interaction studies 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. In addition, results from population pharmacokinetic screening suggest that co-administration of other inducers of drug clearance (efavirenz, nevirapine, phenytoin, dexamethasone, or carbamazepine) with CANCIDAS may also 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 with inducers of drug clearance, such as efavirenz, nevirapine, rifampin, dexamethasone, phenytoin, or carbamazepine, use of a daily dose of 70 mg of CANCIDAS should be considered (see Section III Dosage and Administration).

XI. SIDE EFFECTS

[For alternative tabular version, see ALTERNATIVE Section XXVII.]

In clinical studies, 876 individuals received single or multiple doses of CANCIDAS. There were 125 patients with invasive candidiasis, 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 394 individuals were enrolled in phase I studies. The majority of the patients with *Candida* infections had serious underlying medical conditions (e.g., hematologic or other malignancy, recent major surgery, HIV) 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 patients treated with CANCIDAS (total 425) were typically mild and rarely led to discontinuation.

Common (> 1/100)	General	Fever, headache, abdominal pain, pain, chills
	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)
	Peripheral Vascular	Phlebitis/thrombophlebitis, infused-vein complication
	Skin	Rash, pruritus

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

XIa. Laboratory Test Findings

[For alternative tabular version see ALTERNATIVE Section XXVIIa]

Other drug-related laboratory abnormalities reported were low albumin, low potassium, decreased white blood cells, increased eosinophils, low platelets, decreased neutrophils, increased urinary red blood cells, increased partial thromboplastin time, decreased total serum protein, increased urinary protein, increased prothrombin time, low sodium, increased urinary white blood cells, and low calcium.

XII. OVERDOSAGE

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

XIII. AVAILABILITY

To be filled in locally.

OPTIONAL SECTION

XIVa. DOSAGE AND ADMINISTRATION

[May be added to DOSAGE AND ADMINISTRATION section III General Recommendations]

The safety data on treatment durations longer than 2 weeks are limited; however, available data suggest that CANCIDAS continues to be well tolerated with longer courses of therapy (112 patients received from 15 to 60 days of therapy; 14 patients received from 61 to 162 days of therapy).

XIVb. DOSAGE AND ADMINISTRATION

[May be added to MANDATORY Section III following the table "Preparation of the Patient Infusion Solutions"]

Preparation of the daily 50-mg infusion (using vials with transfer sets)

1. Equilibrate the refrigerated vial of CANCIDAS with transfer set to room temperature.
2. Remove the transfer set cap and mate the vial to the port of a conventional 250 mL infusion bag of Sterile Saline for Injection or Lactated Ringer's Solution. The transfer needle is enclosed in the plastic needle guard. Simultaneous with the insertion of the needle into the bag, the back pressure causes the other end of the needle to pierce the vial stopper, allowing a free flow through the needle between the vial and the diluent bag.
3. The product is mixed by squeezing diluent in and out of the vial to effect dissolution, and the vial contents are allowed to drain back into the infusion bag. After full transfer, the vial and transfer set combination are removed from the infusion bag. This infusion solution must be used within 24 hours if stored at or below 25°C (77°F), or within 48 hours if stored refrigerated at 2 to 8°C (36 to 46°F).

XV. PREGNANCY

[May be added to MANDATORY Section VI, as the second paragraph.]

In rabbits, there were no treatment-related external, visceral, or skeletal fetal morphological findings in an intravenous 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 greater than 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.

XVI. CHEMISTRY

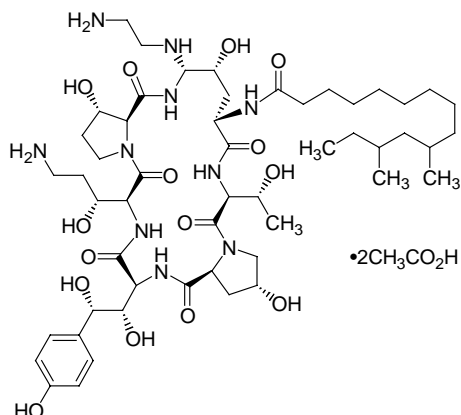
CANCIDAS contains, as the active ingredient, caspofungin acetate, which is described chemically as 1-[(4R,5S)-5-[(2-aminoethyl)amino]-N²-(10,12-dimethyl-1-oxotetradecyl)-4-hydroxy-L-ornithine]-5-[(3R)-3-hydroxy-L-ornithine]pneumocandin B₀ diacetate (salt)

The empirical formula is C₅₂H₈₈N₁₀O₁₅•2C₂H₄O₂

The CAS registry number is 179463-17-3

The formula weight is 1213.42.

The structural formula is:



XVII. COMPOSITION

XVIIa. Active Ingredients:

Each vial of CANCIDAS contains caspofungin acetate as the active ingredient.

XVIIb. Inactive Ingredients:

Each vial of CANCIDAS contains the following inactive ingredients: sucrose, mannitol, glacial acetic acid, and sodium hydroxide (to adjust the pH).

XVIII. STORAGE

Storage of unopened vials

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

Storage of reconstituted CANCIDAS in vials

Reconstituted CANCIDAS may be stored at or below 25°C (77°F) for 24 hours prior to the preparation of the patient infusion solution.

Storage of diluted product for infusion

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

XIX. CLINICAL PHARMACOLOGY

XIXa. 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 many filamentous fungi and yeast. β (1,3)-D-glucan is not present in mammalian cells.

XIXb. Pharmacokinetics

[For a Brief Version of XIXb-1 thru XIXb-4, see ALTERNATIVE section XXIX Pharmacokinetic Properties]

XIXb-1. Absorption

Absorption is not relevant since caspofungin acetate is administered intravenously.

XIXb-2. Distribution

Plasma concentrations of caspofungin decline in a polyphasic manner following single 1-hour intravenous infusions. A short α -phase occurs immediately post-infusion, followed by a β -phase with a 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 by an order of magnitude. An additional γ -phase also occurs (half-life 40-50 hours). Distribution, rather than excretion or biotransformation, is the dominant mechanism influencing plasma clearance. Caspofungin is extensively bound to albumin (approximately 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 [³H] caspofungin acetate. There is little excretion or biotransformation of caspofungin during the first 30 hours after administration.

XIXb-3. 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 postdose), there is a low level (≤ 7 picomoles/mg protein, or $\leq 1.3\%$ of administered dose) of covalent binding of radiolabel in plasma following single-dose administration of [³H] 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 derivatives, including dihydroxyhomotyrosine and N-acetyl-dihydroxyhomotyrosine. These two tyrosine derivatives are found only in urine, suggesting rapid clearance of these derivatives by the kidneys.

XIXb-4. 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 postdose; thereafter drug levels fell more rapidly. In plasma, caspofungin concentrations fell below the limit of quantitation after 6 to 8 days postdose, while radiolabel fell below the limit of quantitation at 22.3 weeks postdose. A small amount of caspofungin is excreted unchanged in urine (approximately 1.4% of dose). Renal clearance of parent drug is low (approximately 0.15 mL/min).

XIXb-5. Characteristics in Patients

Gender

The plasma concentration of caspofungin was similar in healthy men and women on Day 1 following a single 70-mg dose. After 13 daily 50-mg doses, the caspofungin plasma concentration in some women was elevated approximately 20% relative to men.

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.

XIXc. Pharmacodynamics

[For a Brief Version see Alternative XXIX Pharmacodynamic Properties]

Activity in vitro

Caspofungin has *in vitro* activity against *Aspergillus* species (including *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus nidulans*, and *Aspergillus terreus*) and *Candida* species (including *Candida albicans*, *Candida dubliniensis*, *Candida glabrata*, *Candida guilliermondii*, *Candida kefyr*, *Candida krusei*, *Candida lipolytica*, *Candida lusitanae*, *Candida parapsilosis*, *Candida rugosa*, and *Candida tropicalis*). Susceptibility testing was performed according to a modification of both the National Committee for Clinical Laboratory Standards (NCCLS) method M38-A (for *Aspergillus* species) and method M27-A (for *Candida* species). Standardized susceptibility testing methods for β (1,3)-D-glucan synthesis inhibitors have not been established, and results of susceptibility studies do not necessarily correlate with clinical outcome.

Activity in vivo

Caspofungin was active when parenterally administered 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. lusitanae*, *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.

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.

Drug Resistance

Resistance development to caspofungin by *Candida* species occurs very rarely in the laboratory, and clinical *Candida* isolates with intrinsic resistance to caspofungin have not been identified. The relevance to clinical outcome is unknown. *In vitro* drug resistance development to caspofungin in *Aspergillus* species has not been studied. In limited clinical experience, drug resistance in patients with candidiasis or invasive aspergillosis has not been observed. The incidence of drug resistance in various clinical isolates of *Candida* and *Aspergillus* species is unknown.

Drug Interactions

In vitro and *in vivo* studies of caspofungin acetate, in combination with amphotericin B, demonstrate no antagonism of antifungal activity against either *A. fumigatus* or *C. albicans*. Results from *in vitro* studies suggest that there was some evidence of additive/indifferent or synergistic activity against *A. fumigatus* and additive/indifferent activity against *C. albicans*. The clinical significance of these results is unknown.

XIXd. Clinical Studies

[For Brief Versions see ALTERNATIVE Sections XXVIIIa and XXVIIIb]

Invasive Candidiasis

In a Phase III randomized, double-blind study, patients with a proven diagnosis of invasive candidiasis received daily doses of CANCIDAS (50 mg/day following a 70-mg loading dose on Day 1) or amphotericin B deoxycholate (0.6 to 0.7 mg/kg/day for non-neutropenic patients and 0.7 to 1.0 mg/kg/day for neutropenic patients). Patients were stratified by both neutropenic status and APACHE II score. Patients who met the entry criteria and received one or more doses of IV study therapy were included in the primary (modified intention-to-treat [MITT]) analysis of response at the end of IV study therapy. A predefined analysis to support the MITT, the evaluable-patients assessment, included patients who met entry criteria, received IV study therapy for 5 or more days and had a full efficacy evaluation at the end of IV study therapy. A favorable response required both symptom resolution and microbiological clearance of the *Candida* infection.

Of the 239 patients enrolled, 224 (109 treated with CANCIDAS and 115 treated with amphotericin B) met the criteria for inclusion in the MITT analysis. Of these patients, 185 (88 treated with CANCIDAS and 97 treated with amphotericin B) met the criteria for inclusion in the evaluable-patients analysis. The most frequent diagnoses were bloodstream infections (candidemia) (83%) and *Candida* peritonitis (10%). Most infections were caused by *C. albicans* (45%), followed by *C. parapsilosis* (19%), *C. tropicalis* (16%), *C. glabrata* (11%), and *C. krusei* (2%). The favorable response rates at the end of IV study therapy are shown in Table 1.

TABLE 1
Favorable Response Rates to IV Study Therapy
Among Patients with Invasive Candidiasis

	CANCIDAS 50 mg* % (n/m**) [95% CI]	Amphotericin B % (n/m) [95% CI]	Difference (%) after Adjusting for strata [95.6% CI]
MITT analysis	73.4% (80/109) [65.1, 81.7]	61.7% (71/115) [52.8, 70.7]	12.7% [-0.7, 26.0]
Evaluable-patients analysis	80.7% (71/88) [72.4, 89.0]	64.9% (63/97) [55.4, 74.5]	15.4% [1.1, 29.7]

* 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

In neutropenic patients, the favorable response rates at the end of IV study therapy in the CANCIDAS and amphotericin B groups were comparable: 50% (7/14) in the CANCIDAS group and 40% (4/10) in the amphotericin B group. In patients with high (>20) APACHE II scores at study entry, favorable response rates in the CANCIDAS and amphotericin B group were similar: 57.1% (12/21) in the CANCIDAS group and 43.5% (10/23) in the amphotericin B group. Response rates were also consistent across all identified *Candida* species. For all other efficacy time points (Day 10 of IV study therapy, end of all antifungal therapy, 2-week post-therapy follow-up, and 6- to 8-week post-therapy follow-up), CANCIDAS was as effective as amphotericin B. CANCIDAS was also comparable to amphotericin B with regard to relapse or survival rates.

CANCIDAS was comparable to amphotericin B in the treatment of invasive candidiasis at the end of IV study therapy in the primary (MITT) efficacy analysis. In a predefined efficacy analysis of evaluable patients to support the MITT, CANCIDAS was statistically superior to amphotericin B at the end of IV study therapy.

Candidemia

Of the 224 patients from the invasive candidiasis study who met the criteria for inclusion in the MITT analysis, 186 patients (92 treated with CANCIDAS and 94 treated with amphotericin B) had candidemia. Of these patients, 150 (71 treated with CANCIDAS and 79 treated with amphotericin B) met the criteria for inclusion in the evaluable-patients analysis. The favorable response rates at the end of IV study therapy for patients with candidemia are shown in Table 2.

TABLE 2
Favorable Response Rates to IV Study Therapy
Among Patients with Candidemia

	CANCIDAS 50 mg* % (n/m**) [95% CI]	Amphotericin B % (n/m) [95% CI]	Difference (%) after adjusting for strata [95.6% CI]
MITT analysis	71.7% (66/92) [62.5, 81.0]	62.8% (59/94) [52.9, 72.6]	10.0% [-4.5, 24.5]
Evaluable-patients 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

In both the MITT and evaluable-patients efficacy analyses, CANCIDAS was comparable to amphotericin B in the treatment of candidemia at the end of IV study therapy.

Esophageal Candidiasis

Three comparative studies were conducted to evaluate the efficacy of CANCIDAS for the treatment of esophageal candidiasis. One study compared CANCIDAS to IV fluconazole. In addition, two dose-ranging studies compared different doses of CANCIDAS to amphotericin B. A total of 393 patients with esophageal candidiasis were enrolled in these 3 studies (CANCIDAS, n=222; fluconazole, n=94; amphotericin B, n=77). In all 3 studies, patients were required to have symptoms and microbiological documentation of esophageal candidiasis; and most patients had advanced AIDS (with CD4 counts <50/mm³). Disease severity was determined by esophagoscopy (endoscopy).

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 7 to 21 days. A favorable 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. The proportion of patients with a favorable 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.

Two double-blind, comparative dose-ranging studies evaluated 3 different doses of CANCIDAS (35, 50, 70 mg/day) and amphotericin B (0.5 mg/kg/day). The proportion of patients with a favorable overall response in the group receiving CANCIDAS 50 mg/day was 34/46 (73.9%) for study 1, and 18/20 (90.0%) for study 2; the proportion of patients with a favorable overall response in the group receiving amphotericin B was 34/54 (63.0%) for study 1 and 14/23 (60.9%) for study 2. Doses of CANCIDAS above 50 mg daily provided no additional benefit in esophageal candidiasis.

Oropharyngeal Candidiasis

Evidence to support the efficacy of CANCIDAS for the treatment of oropharyngeal candidiasis was derived from two groups of patients enrolled in the 3 comparative studies described above. The first group, derived from the patients in these comparative studies, had both oropharyngeal and esophageal disease

(n=173); the second group had only oropharyngeal disease (n=52). A favorable response was defined as complete resolution of all symptoms of oropharyngeal disease and all visible oropharyngeal lesions.

Of the fifty-two patients who had only oropharyngeal disease and who were treated for 7 to 10 days, 14 patients received CANCIDAS at the recommended dose of 50 mg/day. The favorable response rates were 92.9% (13/14) for CANCIDAS and 66.7% (8/12) for amphotericin B dosed at 0.5 mg/kg/day.

Results from patients with both oropharyngeal and esophageal disease provide additional evidence that CANCIDAS (50 mg/day; n=67) is effective for the treatment of oropharyngeal candidiasis, with results comparable to amphotericin B or fluconazole. Doses of CANCIDAS above 50 mg daily provided no additional benefit in oropharyngeal candidiasis.

Invasive Aspergillosis

Sixty-nine patients between the ages of 18 and 80 with invasive aspergillosis 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 7 days or more 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 of 2.5 mg/dL or more while on therapy), other acute reactions, or infusion-related toxicity. To be included in the study, patients with pulmonary disease must have had invasive aspergillosis classified as 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). 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 greater than 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 greater than 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.

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

A medical chart review of 206 patients with invasive aspergillosis was also conducted to assess the response to standard (noninvestigational) therapies. Patient characteristics and important risk factors in this review were similar to those of patients enrolled in the open-label noncomparative study (see above), and the same rigorous definitions of diagnosis and outcome were used. To be included in this study, patients had to have had invasive aspergillosis and to have received at least 7 days of standard antifungal therapy. The favorable response rate from this historical control study was 17% (35/206) for standard therapy compared to the favorable response rate of 41% (26/63) for CANCIDAS in the open-label noncomparative study. The results of the multivariate analyses demonstrated an odds ratio of greater than 3 for CANCIDAS, with a 95% confidence interval excluding 1, suggesting a benefit of therapy with CANCIDAS.

XX. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No data are available on whether CANCIDAS impairs the ability to drive or operate machinery.

XXI. INFORMATION FOR PATIENTS

[For inclusion in Physicians Circular only. Not to be substituted for a Patient Package Insert.]

Not applicable.

XXII. ANIMAL TOXICOLOGY

XXIIa. Acute Toxicity

The approximate intravenous lethal dose₅₀ (LD₅₀) for female mice and rats was calculated as 19 and 38 mg/kg, respectively.

XXIIb. 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 produced with a structural analog of caspofungin acetate in monkeys were reversed upon injection of cyproheptadine.

In 5-, 14-, and 27-week intravenous toxicity studies in monkeys, ALT and/or AST levels increased slightly, but these levels returned to baseline or remained slightly elevated over the course of the studies. In one 5-week study, scattered small foci of subcapsular necrosis were observed microscopically in the livers of some animals; however, this histopathological finding was not seen in other studies of up to 27 weeks duration at the same or higher doses. The no-effect level for serum transaminase elevations after

intravenous treatment was 1.5 mg/kg/day in monkeys, and greater than 7.2 mg/kg/day in rats (the highest dose tested).

During the 5-, 14-, and 27-week intravenous toxicity studies in rats and monkeys, clinical and histopathological signs of injection-site irritation were observed. 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). Effective pre- and postdose flushing of catheter lines minimized injection-site irritation in animal studies.

XXIc. Carcinogenicity

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

XXId. 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.

XXIe. Reproduction

Female rats administered 0.5, 2, and 5 mg/kg/day of caspofungin acetate intravenously 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.

XXIf. Development

In rats, there were no developmental effects at a dose of 2 mg/kg/day. 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, caspofungin caused decreases in fetal body weights and an increase in the incidence of incomplete ossification of the skull and torso. In addition, at this same maternally toxic dose, there was an increase in the incidence of cervical rib in rats.

In rabbits, there were no treatment-related external, visceral, or skeletal fetal morphological findings in an intravenous toxicity study where caspofungin acetate was administered to pregnant rabbits at dosages of 1, 3, and 6 mg/kg/day on gestation days 7 through 20. Therefore, the no-effect level for developmental toxicity was greater than 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. Pregnant rabbits administered 5 mg/kg/day had plasma exposures approximately 1.5 times the plasma exposure seen in humans administered 70 mg.

Caspofungin acetate has been shown to cross the placental barrier in animal studies.

ALTERNATIVE SECTION

XXIII. DOSAGE AND ADMINISTRATION

[May be substituted for MANDATORY section III]

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.

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 and Oropharyngeal Candidiasis

Fifty (50) mg daily should be administered by slow intravenous infusion over approximately 1 hour.

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. Although there is no information to demonstrate an increase in efficacy with higher doses, available safety data suggest that an increase in dose to 70 mg daily may be considered in patients without evidence of clinical response in whom CANCIDAS has been well tolerated.

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 candidiasis or 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).

Concomitant Therapy with Inducers of Drug Clearance

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

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

1. Equilibrate the refrigerated vial of CANCIDAS to room temperature.
2. Aseptically add 10.5 mL of "step-1" diluent ^a (see *Preparation notes* below) to the vial. ^{b,c}
3. Aseptically transfer 10 mL^d of reconstituted CANCIDAS to an intravenous (IV) bag (or bottle) containing a recommended "step-2" diluent ^{e,f} (see *Preparation notes* below). 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 (Conventional Vial)

1. Equilibrate the refrigerated conventional vial of CANCIDAS to room temperature.
2. Aseptically add 10.5 mL of a recommended “step-1” diluent ^a (see Preparation notes below) to the vial. ^{b,c}
3. Aseptically transfer 10 mL^d of reconstituted CANCIDAS to an IV bag (or bottle) containing 250 mL of a “step-2” diluent ^{e,f} (see Preparation notes below). 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

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 a “step-2” diluent.

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 (at 5 mg/mL) to 100 mL of a “step-2” diluent (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 of “step-2” diluent or, if medically necessary, to 100 mL of “step-2” diluent.

Preparation notes:

- a. The “step-1” diluents are: Sterile Water for Injection, Bacteriostatic Water for Injection with methylparaben and propylparaben, or Bacteriostatic Water for Injection with 0.9% benzyl alcohol. Do not mix with diluents containing dextrose (α -D-glucose). This reconstituted solution may be stored for up to 24 hours at $\leq 25^{\circ}\text{C}$ ($\leq 77^{\circ}\text{F}$).
- b. The white to off-white cake will dissolve completely. Mix gently until a clear solution is obtained.
- c. 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 precipitated.
- d. CANCIDAS is formulated to provide the full labeled vial dose (70 mg or 50 mg) when 10 mL is withdrawn from the vial.
- e. The “step-2” diluents are: 0.9, 0.45, and 0.225% Sterile Saline for Injection, or Lactated Ringer’s Solution. Do not mix with diluents containing dextrose (α -D-glucose).
- f. This infusion solution must be used within 24 hours if stored at $\leq 25^{\circ}\text{C}$ ($\leq 77^{\circ}\text{F}$) or within 48 hours if stored refrigerated at 2 to 8°C (36 to 46°F).

CANCIDAS Concentrations

Dose	Reconstituted Solution Concentration	Infusion Volume	Infusion Solution Concentration
70-mg initial dose	7.0 mg/mL	260 mL	0.27 mg/mL
50-mg daily dose	5.0 mg/mL	260 mL	0.19 mg/mL
70-mg initial dose* (from two 50 mg vials)	5.0 mg/mL	264 mL	0.27 mg/mL
50-mg daily dose* (reduced volume)	5.0 mg/mL	110 mL	0.45 mg/mL
35-mg daily dose* (from one 50 mg vial) for Moderate Hepatic Insufficiency	5.0 mg/mL or 5.0 mg/mL	257 mL or 107 mL	0.14 mg/mL or 0.33 mg/mL

* See preceding text for these special situations

XXIV. PREGNANCY

[Includes Pregnancy Category and preclinical study information]

Pregnancy Category C. 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 intravenous toxicity study where caspofungin acetate was administered to pregnant rabbits at dosages of 1, 3, and 6 mg/kg/day on gestation days 7 through 20. Therefore, the no-effect level for developmental toxicity was >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 administered 5 mg/kg/day.

Caspofungin has been shown to cross the placental barrier in animal studies.

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.

XXV. PRECAUTIONS

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 SIDE EFFECTS XXVII). Hence, concomitant use of CANCIDAS with cyclosporine is not recommended until multiple-dose use in patients is studied.

XXVI. DRUG INTERACTIONS

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 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%. These AUC increases were probably due to reduced uptake of caspofungin by the liver.

CANCIDAS reduced the blood AUC of tacrolimus (FK-506, Prograf®²) by approximately 20%, maximal 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.

Population pharmacokinetic screening of caspofungin concentrations in patients receiving other concomitant medications indicate that elevations in plasma caspofungin levels due to drug interactions, as was seen in the formal drug interaction study with cyclosporine, are uncommon. Results from two clinical drug interaction studies 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. In addition, results from population pharmacokinetic screening suggest that co-administration of other inducers of drug clearance (efavirenz, nevirapine, phenytoin, dexamethasone, or carbamazepine) with CANCIDAS may also 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. 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 should be considered.

XXVII. SIDE EFFECTS

The overall safety of caspofungin was assessed in 876 individuals who received single or multiple doses of caspofungin acetate. There were 125 patients with invasive candidiasis, 285 patients with esophageal and/or oropharyngeal candidiasis and 72 patients with invasive aspergillosis enrolled in phase II and phase III studies. The remaining 394 individuals were enrolled in phase I studies. The majority of the patients with *Candida* infections had serious underlying medical conditions (e.g., hematologic or other malignancy, recent major surgery, HIV) requiring multiple concomitant medications. Patients in the noncomparative *Aspergillosis* study often had serious predisposing medical conditions (e.g., bone marrow or peripheral stem cell transplants, hematologic malignancies, solid tumors or organ transplants) requiring multiple concomitant medications.

In the randomized, double-blinded invasive candidiasis study, patients received either CANCIDAS 50 mg/day (following a 70-mg loading dose) or amphotericin B 0.6 to 1.0 mg/kg/day. Drug-related clinical adverse experiences occurring in $\geq 2\%$ of the patients in either treatment group are presented in Table 3.

² Registered trademark of Fujisawa Healthcare, Inc.

TABLE 3
Drug-Related Clinical Adverse Experiences Among Patients with Invasive Candidiasis*
Incidence $\geq 2\%$ for at least one treatment group by Body System

	CANCIDAS 50 mg** N=114 (percent)	Amphotericin B N=125 (percent)
Body as a Whole		
Chills	5.3	26.4
Fever	7.0	23.2
Cardiovascular System		
Hypertension	1.8	6.4
Hypotension	0.9	2.4
Tachycardia	1.8	10.4
Peripheral Vascular System		
Phlebitis/thrombophlebitis	3.5	4.8
Digestive System		
Diarrhea	2.6	0.8
Jaundice	0.9	3.2
Nausea	1.8	5.6
Vomiting	3.5	8.0
Metabolic/Nutritional/Immune		
Hypokalemia	0.9	5.6
Nervous System & Psychiatric		
Tremor	1.8	2.4
Respiratory System		
Tachypnea	0.0	10.4
Skin & Skin Appendage		
Erythema	0.0	2.4
Rash	0.9	3.2
Sweating	0.9	3.2
Urogenital System		
Renal insufficiency	0.9	5.6
Renal insufficiency, acute	0.0	5.6

* 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%).

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

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

	CANCIDAS 50 mg (N=83) (percent)	Fluconazole 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	0.0	0.0	0.0	0.0	6.7
Chills	0.0	0.0	2.5	1.5	75.3
Edema/swelling	0.0	0.0	0.0	0.0	5.6
Edema, facial	0.0	0.0	0.0	3.1	0.0
Fever	3.6	1.1	21.3	26.2	69.7
Flu-like illness	0.0	0.0	0.0	3.1	0.0
Malaise	0.0	0.0	0.0	0.0	5.6
Pain	0.0	0.0	1.3	4.6	5.6
Pain, abdominal	3.6	2.1	2.5	0.0	9.0
Warm sensation	0.0	0.0	0.0	1.5	4.5
Cardiovascular System					
Tachycardia	0.0	0.0	1.3	0.0	4.5
Vasculitis	0.0	0.0	0.0	0.0	3.4
Peripheral Vascular					
Infused vein complication	12.0	8.5	2.5	1.5	0.0
Phlebitis/thrombophlebitis	15.7	8.5	11.3	13.8	22.5
Digestive System					
Anorexia	0.0	0.0	1.3	0.0	3.4
Diarrhea	3.6	2.1	1.3	3.1	11.2
Gastritis	0.0	2.1	0.0	0.0	0.0
Nausea	6.0	6.4	2.5	3.1	21.3
Vomiting	1.2	3.2	1.3	3.1	13.5
Musculoskeletal System					
Myalgia	1.2	0.0	0.0	3.1	2.2
Pain, back	0.0	0.0	0.0	0.0	2.2
Pain, musculoskeletal	0.0	0.0	1.3	0.0	4.5
Hemic & Lymphatic System					
Anemia	0.0	0.0	3.8	0.0	9.0
Metabolic/Nutritional/Immune					
Anaphylaxis	0.0	0.0	0.0	0.0	2.2
Nervous System & Psychiatric					
Dizziness	0.0	2.1	0.0	1.5	1.1
Headache	6.0	1.1	11.3	7.7	19.1
Insomnia	1.2	0.0	0.0	0.0	2.2
Paresthesia	0.0	0.0	1.3	3.1	1.1
Tremor	0.0	0.0	0.0	0.0	7.9
Respiratory System					
Tachypnea	0.0	0.0	1.3	0.0	4.5
Skin & Skin Appendage					
Erythema	1.2	0.0	1.3	1.5	7.9
Induration	0.0	0.0	0.0	3.1	6.7
Pruritus	1.2	0.0	2.5	1.5	0.0
Rash	0.0	0.0	1.3	4.6	3.4
Sweating	0.0	0.0	1.3	0.0	3.4

* 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.

In the open-label, noncomparative aspergillosis study, in which 69 patients received CANCIDAS (70-mg loading dose on Day 1 followed by 50 mg daily), the following drug-related clinical adverse experiences were observed with an incidence of $\geq 2\%$: fever (2.9%), infused-vein complications (2.9%), nausea (2.9%), vomiting (2.9%) and flushing (2.9%).

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

XXVIIa. Laboratory Test Findings

Drug-related laboratory adverse experiences occurring in $\geq 2\%$ of the patients with invasive candidiasis are presented in Table 5.

TABLE 5
Drug-Related Laboratory Adverse Experiences Among Patients with Invasive Candidiasis*
Incidence $\geq 2\%$ for at least one treatment group by Laboratory Test Category

	CANCIDAS 50 mg** N=114 (percent)	Amphotericin B N=125 (percent)
Blood Chemistry		
ALT increased	3.7	8.1
AST increased	1.9	9.0
Blood urea increased	1.9	15.8
Direct serum bilirubin increased	3.8	8.4
Serum alkaline phosphatase increased	8.3	15.6
Serum bicarbonate decreased	0.0	3.6
Serum creatinine increased	3.7	22.6
Serum phosphate increased	0.0	2.7
Serum potassium decreased	9.9	23.4
Serum potassium increased	0.9	2.4
Total serum bilirubin increased	2.8	8.9
Hematology		
Hematocrit decreased	0.9	7.3
Hemoglobin decreased	0.9	10.5
Urinalysis		
Urine protein increased	0.0	3.7

* 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 laboratory adverse experiences was significantly lower among patients receiving CANCIDAS (24.3%) than among patients receiving amphotericin B (54.0%).

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.

Drug-related laboratory abnormalities occurring in $\geq 2\%$ of patients with esophageal and/or oropharyngeal candidiasis are presented in Table 6.

TABLE 6
Drug-Related Laboratory Abnormalities Reported Among Patients with Oropharyngeal and/or Esophageal Candidiasis (comparative studies)*
Incidence $\geq 2\%$ (for at least one treatment dose) by Laboratory Test Category

	CANCIDAS 50 mg (N=163) (percent)	CANCIDAS 70 mg (N=65) (percent)	Fluconazole 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	0.0	0.0	1.2	10.3
Direct serum bilirubin increased	0.6	0.0	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	0.0	0.0	6.6
Serum calcium decreased	1.9	0.0	3.2	1.1
Serum creatinine increased	0.0	1.5	2.2	28.1
Serum potassium decreased	3.7	10.8	4.3	31.5
Serum potassium increased	0.6	0.0	2.2	1.1
Serum sodium decreased	1.9	1.5	3.2	1.1
Serum uric acid increased	0.6	0.0	0.0	3.4
Total serum bilirubin increased	0.0	0.0	3.2	4.5
Total serum protein decreased	3.1	0.0	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	0.0	1.6	2.2	0.0
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	0.0	2.3
WBC count decreased	6.2	4.6	8.6	7.9
Urinalysis				
Urine blood increased	0.0	0.0	0.0	4.0
Urine casts increased	0.0	0.0	0.0	8.0
Urine pH increased	0.8	0.0	0.0	3.6
Urine protein increased	1.2	0.0	3.3	4.5
Urine RBC's increased	1.1	3.8	5.1	12.0
Urine WBC's increased	0.0	7.7	0.0	24.0

* 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.

Drug-related laboratory abnormalities reported with an incidence $\geq 2\%$ 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%).

XXVIII. CLINICAL STUDIES - Brief Versions

XXVIIIa. Clinical Studies - Brief Version A

[A version with more detail can be found in OPTIONAL Section XIXd]

[A shorter version can be found in ALTERNATIVE Section XXVIIIb - the next section]

[Note that the text on invasive candidiasis in this section is identical to that found in Section XXVIIIb.]

Invasive Candidiasis

Two hundred thirty-nine patients were enrolled in a 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 (73%

[80/109]) and amphotericin B (62% [71/115]). 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 (favorable response rate 81% [71/88]) was statistically superior to amphotericin B (65% [63/97]) at the end of IV study therapy. Among patients with candidemia, the favorable response rates at the end of IV study therapy were 72% (66/92) in the CANCIDAS group and 63% (59/94) in the amphotericin B group in the primary efficacy analysis, and were 80% (57/71) in the CANCIDAS group and 65% (51/79) in the amphotericin B group in the predefined efficacy analysis to support the primary analysis. In both analyses, CANCIDAS was comparable to amphotericin B in the treatment of candidemia at the end of IV study therapy.

Esophageal Candidiasis

Three comparative studies (enrolling a total of 393 patients) were conducted to evaluate the efficacy of CANCIDAS for the treatment of esophageal candidiasis (EC). All patients had symptoms and microbiological documentation of EC and most had advanced AIDS (CD4 counts less than 50/mm³). In all studies, a favorable overall response required both complete resolution of symptoms and significant endoscopic improvement 5 to 7 days following completion of study therapy. In a randomized, double-blind study comparing CANCIDAS 50 mg/day versus IV fluconazole 200 mg/day, patients with EC were treated for 7 to 21 days. The proportion of patients with favorable overall responses were comparable: CANCIDAS 82% versus fluconazole 85%. The proportion of patients with a favorable symptom response (CANCIDAS 90% versus fluconazole 89%) or a favorable endoscopic response (CANCIDAS 85% versus fluconazole 86%) were also comparable.

Two additional double-blind, comparative dose-ranging studies evaluated 3 different doses of CANCIDAS (35, 50, 70 mg/day) and amphotericin B (0.5 mg/kg/day). In the first study, the favorable overall response was 74% (34/46) for CANCIDAS 50 mg/day, and 63% (34/54) for amphotericin B. In the second study, the favorable overall responses were 90% (18/20) for CANCIDAS 50 mg/day, and 61% (14/23) for amphotericin B. Doses of CANCIDAS above 50 mg daily provided no additional benefit in EC.

Oropharyngeal Candidiasis

Evidence to support the efficacy of CANCIDAS for the treatment of oropharyngeal candidiasis (OPC) was derived from two groups of patients enrolled in the 3 comparative studies described above. The first group had both OPC and EC (n=173), the second group only OPC (n=52). A favorable response was defined as complete resolution of all symptoms of oropharyngeal disease and all visible oropharyngeal lesions.

Of the patients who had only OPC and who were treated for 7 to 10 days, 14 patients received CANCIDAS at the recommended dose of 50 mg/day. The favorable response rates were 93% (13/14) for CANCIDAS and 67% (8/12) for amphotericin B (0.5 mg/kg/day).

Results from patients with both OPC and EC provide additional evidence that CANCIDAS (50 mg/day) is effective for the treatment of oropharyngeal candidiasis, with results comparable to amphotericin B or fluconazole. Doses of CANCIDAS above 50 mg daily provided no additional benefit in OPC.

Invasive Aspergillosis

Sixty-nine patients between the ages of 18 and 80 with invasive aspergillosis were enrolled in an open-label, noncomparative study to evaluate the safety, tolerability, and efficacy of CANCIDAS. Enrolled patients were either refractory to (disease progression or failure to improve with other therapies) or intolerant of (nephrotoxicity, infusion-related reactions, or other acute reactions) other antifungal therapy(ies). Patients with pulmonary disease must have had invasive aspergillosis classified as either 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). Patients with extrapulmonary disease had to have definite invasive aspergillosis. The definitions were modeled after the Mycoses Study Group Criteria.³ Patients were

³ 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

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. Eighty-four percent of patients were refractory to previous antifungal therapy and most had hematologic malignancies or allogeneic bone marrow transplant.

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 more than 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. Among patients with extrapulmonary disease, 2 of 8 patients who also had definite, probable, or possible CNS involvement had a favorable response.

A medical chart review of 206 patients with invasive aspergillosis was also conducted to assess the response to standard (noninvestigational) therapies. Patient characteristics and important risk factors were well balanced between patients enrolled in the aspergillosis study and the historical control study. The favorable response rate from this historical control study was 17% (35/206) for standard therapy compared to 41% (26/63) for CANCIDAS in the open-label noncomparative study. The results of the multivariate analyses demonstrated an odds ratio of greater than 3 for CANCIDAS, with the 95% confidence interval excluding 1, suggesting a benefit of therapy with CANCIDAS.

XXVIIIb. Clinical Studies - Brief Version B

[Versions with greater detail can be found in ALTERNATIVE Section XXVIIIa and OPTIONAL Section XIXd]

[Note that the text on invasive candidiasis in this section is identical to that found in Section XXVIIIa.]

Invasive Candidiasis

Two hundred thirty-nine patients were enrolled in a 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 (73% [80/109]) and amphotericin B (62% [71/115]). 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 (favorable response rate 81% [71/88]) was statistically superior to amphotericin B (65% [63/97]) at the end of IV study therapy. Among patients with candidemia, the favorable response rates at the end of IV study therapy were 72% (66/92) in the CANCIDAS group and 63% (59/94) in the amphotericin B group in the primary efficacy analysis, and were 80% (57/71) in the CANCIDAS group and 65% (51/79) in the amphotericin B group in the predefined efficacy analysis to support the primary analysis. In both analyses, CANCIDAS was comparable to amphotericin B in the treatment of candidemia at the end of IV study therapy.

Esophageal Candidiasis

Studies were conducted to evaluate the efficacy of CANCIDAS for the treatment of esophageal candidiasis (EC). In all studies, all patients had symptoms and microbiological documentation of EC, and most had advanced AIDS (CD4 counts less than 50/mm³). In a large, randomized double-blind study, patients with EC were treated for 7 to 21 days with CANCIDAS 50 mg/day or IV fluconazole 200 mg/day. The proportion of patients with overall favorable responses (resolution of symptoms and improvement of lesions on endoscopy) were comparable: CANCIDAS 82% versus fluconazole 85%.

Two additional dose-ranging studies evaluated 3 different doses of CANCIDAS (35, 50, 70 mg/day) and amphotericin B (0.5 mg/kg/day). In the first study, the favorable overall response was 74% (34/46) for CANCIDAS (50 mg/day) and 63% (34/54) for amphotericin B. In the second study, the favorable overall responses were 90% (18/20) for CANCIDAS 50 mg/day and 61% (14/23) for amphotericin B. Doses of CANCIDAS above 50 mg daily provided no additional benefit in EC.

Oropharyngeal Candidiasis

Evidence to support the efficacy of CANCIDAS for the treatment of oropharyngeal candidiasis (OPC) was derived from patients enrolled in the studies described above. In all patients, a favorable response was defined as complete resolution of all symptoms of oropharyngeal disease and all visible oropharyngeal lesions. One group had only OPC (n=52), and the other both OPC and EC (n=173). Of the patients who had only OPC and who were treated for 7 to 10 days, 14 patients received CANCIDAS at the recommended dose of 50 mg/day. The favorable response rates were 93% (13/14) for CANCIDAS and 67% (8/12) for amphotericin B (0.5 mg/kg/day).

Results from patients with both OPC and EC provide additional evidence that CANCIDAS (50 mg/day) is effective for the treatment of oropharyngeal candidiasis, with results comparable to amphotericin B or fluconazole. Doses of CANCIDAS above 50 mg daily provided no additional benefit in OPC.

Invasive Aspergillosis

Sixty-nine patients (age range: 18 to 80) with pulmonary or extrapulmonary invasive aspergillosis (IA) were enrolled in an open-label, noncomparative study to evaluate the safety, tolerability, and efficacy of CANCIDAS. Enrolled patients were either refractory to (disease progression or failure to improve with other therapies) or intolerant of (nephrotoxicity, infusion-related reactions, or other acute reactions) other antifungal therapy(ies). Pulmonary disease patients had definite or probable IA. Patients with extrapulmonary disease had definite IA. Patients were administered a single 70-mg loading dose followed by 50 mg daily. The mean duration of therapy was 33.7 days (range: 1 to 162 days). Eighty-four percent of patients were refractory to previous antifungal therapy and most had hematologic malignancies or allogeneic bone marrow transplant.

An independent expert panel evaluated patient data and determined that 41% (26/63) of patients receiving at least one dose of CANCIDAS had a favorable response, 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. For those patients who received more than 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.

A medical chart review of 206 patients with IA (well-matched to the study above) was also conducted to assess the response to standard (noninvestigational) therapies. The favorable response rate from this historical control study was 17% (35/206) for standard therapy compared to 41% (26/63) for CANCIDAS in the open-label noncomparative study. The results of the multivariate analyses demonstrated an odds ratio of greater than 3 for CANCIDAS, with the 95% confidence interval excluding 1, suggesting a beneficial effect of therapy with CANCIDAS.

Pharmacodynamic properties

Pharmacotherapeutic group: Antifungal

Caspofungin acetate is a semisynthetic lipopeptide (echinocandin) compound synthesized from a fermentation product of *Glarea lozoyensis*. 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.

Pharmacological studies indicate that caspofungin has *in vitro* activity against various pathogenic fungi of the *Aspergillus* and *Candida* species. Standardized susceptibility testing methods for β (1,3)-D-glucan synthesis inhibitors have not been established, and results of susceptibility studies do not necessarily correlate with clinical outcome.

Pharmacokinetic properties

Plasma concentrations of caspofungin decline in a polyphasic manner following single 1-hour intravenous infusions. A short α -phase occurs immediately postinfusion, followed by a β -phase with a half-life of 9 to 11 hours. An additional γ -phase also occurs (half-life of 40-50 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. 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.