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PRODUCT CIRCULAR

CANCIDAS®

(caspofungin acetate) **Powder for injection**

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

II. CLINICAL PHARMACOLOGY

IIa. 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.

IIb. Pharmacokinetics

IIb-1. Absorption

Absorption is not relevant since caspofungin acetate is administered intravenously.

IIb-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 10-fold. An additional γ -phase also occurs with 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 [^{3}H] caspofungin acetate. There is little excretion or biotransformation of caspofungin during the first 30 hours after administration.

IIb-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 ≤ 1.3% of administered dose) of covalent binding of radiolabel in plasma following single-dose administration of [^{3}H] caspofungin acetate, which may be due to two reactive intermediates formed during the chemical degradation of caspofungin. Additional metabolism involves hydrolysis into constitutive amino acids and their 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.

IIb-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).

IIb-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 adult patients with mild hepatic insufficiency (Child-Pugh score 5 to 6) were increased by approximately 55% in AUC compared to healthy control subjects. In a 14-day multiple-dose study (70 mg on Day 1 followed by 50 mg daily thereafter), plasma concentrations in adult patients with mild hepatic insufficiency were increased modestly (19 to 25% in AUC) on Days 7 and 14 relative to healthy control subjects.

Pediatric Patients

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

- In adolescents (ages 12 to 17 years) receiving caspofungin at 50 mg/m^2 daily (maximum 70 mg daily), the caspofungin plasma $AUC_{0\text{-}24hr}$ was generally comparable to that seen in adults receiving caspofungin at 50 mg daily. All adolescents received doses >50 mg daily, and, in fact, 6 of 8 received the maximum dose of 70 mg/day. The caspofungin plasma concentrations in these adolescents were reduced relative to adults receiving 70 mg daily, the dose most often administered to adolescents.
- In children (ages 2 to 11 years) receiving caspofungin at 50 mg/m^2 daily (maximum 70 mg daily), the caspofungin plasma $AUC_{0\text{-}24hr}$ after multiple doses was comparable to that seen in adults receiving caspofungin at 50 mg/day. On the first day of administration, $AUC_{0\text{-}24hr}$ was somewhat higher in children than adults for these comparisons (37% increase for the 50 mg/m^2/day to 50 mg/day comparison). However, it should be recognized that the AUC values in these children on Day 1 were still less than those seen in adults at steady-state conditions.
- In young children and toddlers (ages 12 to 23 months) receiving caspofungin at 50 mg/m^2 daily (maximum 70 mg daily), the caspofungin plasma $AUC_{0\text{-}24hr}$ after multiple doses was comparable to that seen in adults receiving caspofungin at 50 mg/day and to that in older children (2 to 11 years of age) receiving the 50 mg/m^2 daily dose.
- Overall, the available pharmacokinetic, efficacy, and safety data are limited in patients 3 to 10 months of age. Pharmacokinetic data from one 10-month old child receiving the 50 mg/m^2 daily dose indicated an $AUC_{0\text{-}24hr}$ within the same range as that observed in older children and adults at the 50 mg/m^2 and the 50 mg dose, respectively, while in one 6-month old child receiving the 50 mg/m^2 dose, the $AUC_{0\text{-}24hr}$ was somewhat higher.
- In neonates and infants (<3 months) receiving caspofungin at 25 mg/m^2 daily, caspofungin peak concentration (C_{1hr}) and caspofungin trough concentration (C_{24hr}) after multiple doses were comparable to that seen in adults receiving caspofungin at 50 mg daily. On Day 1, C_{1hr} was comparable and C_{24hr} modestly elevated (36%) in these neonates and infants relative to adults. $AUC_{0\text{-}24hr}$ measurements were not performed in this study due to the sparse plasma sampling. Of note, the efficacy and safety of CANCIDAS have not been adequately studied in prospective clinical trials involving neonates and infants under 3 months of age.

IIc. Pharmacodynamics

Activity in vitro

Caspofungin has *in vitro* activity against *Aspergillus* species (including *Aspergillus fumigatus, Aspergillus flavus, Aspergillus niger, Aspergillus nidulans, Aspergillus terreus,* and *Aspergillus candidus*) and *Candida* species (including *Candida albicans, Candida dubliniensis, Candida glabrata, Candida guilliermondii, Candida kefyr, Candida krusei, Candida lipolytica, Candida lusitaniae, Candida parapsilosis, Candida rugosa,* and *Candida tropicalis*). Susceptibility testing was performed according to a modification of both the Clinical and Laboratory Standards Institute (CLSI, formerly known as the National Committee for Clinical Laboratory Standards [NCCLS]) method M38-A2 (for *Aspergillus* species) and method M27-A3 (for *Candida* species).

Interpretive standards (or breakpoints) for caspofungin against *Candida* species are applicable only to tests performed using CLSI microbroth dilution reference method M27-A3 for minimum inhibitory concentrations (MIC) read as a partial inhibition endpoint at 24 hours. The MIC values for caspofungin using CLSI microbroth dilution reference method M27-A3 should be interpreted according to the criteria provided in Table 1 below (CLSI M27-S3).

TABLE 1

Susceptibility Interpretive Criteria for Caspofungin against *Candida* Species

Pathogen	Broth Microdilution MIC*,† (µ g/mL) at 24 hours			
	Susceptible	Indeterminate	Resistant	Non-susceptible
Candida species	≤ 2	-	-	>2

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

† There is no Resistant category assigned for the echinocandin agents; isolates with higher MICs may be described as Non-susceptible.

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

Standardized techniques for susceptibility testing have been established for yeasts by EUCAST. No standardized techniques for susceptibility testing or interpretive breakpoints have been established for *Aspergillus* species and other filamentous fungi using either the CLSI or EUCAST method.

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. lusitaniae*, *C. parapsilosis*, or *C. tropicalis* in which the endpoint was clearance of *Candida* from target organs. In a lethal, rat pulmonary-infection model with *A. fumigatu*s, 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

A caspofungin MIC of ≤ 2 µ g/mL ("Susceptible" per Table 1) using the CLSI M27-A3 method indicates that the *Candida* isolate is likely to be inhibited if caspofungin therapeutic concentrations are achieved. Breakthrough infections with *Candida* isolates requiring caspofungin concentrations >2 µ g/mL for growth inhibition have developed in a mouse model of *C. albicans* infection. Isolates of *Candida* with reduced susceptibility to caspofungin have been identified in a small number of patients during treatment (MICs for caspofungin >2 µ g/mL using standardized MIC testing techniques approved by the CLSI). Some of these isolates had mutations in the FKS1/FKS2 gene. Although the incidence is rare, these cases have been routinely associated with poor clinical outcomes.

In clinical experience, drug resistance in patients with invasive aspergillosis has been observed. The mechanism of resistance has not been established.

The incidence of drug resistance in various clinical isolates of *Candida* and *Aspergillus* species is rare.

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. albican*s. 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. albican*s. The clinical significance of these results is unknown.

III. INDICATIONS

CANCIDAS is indicated in adult and pediatric patients (12 months and older) for:

- Empirical therapy for presumed fungal infections (such as *Candida* or *Aspergillus*) in febrile, neutropenic patients, whose fever has failed to respond to broad-spectrum antibiotics.

- Treatment of Candidemia and the following *Candida* infections: intra-abdominal abscesses, peritonitis and pleural space infections. CANCIDAS has not been studied in endocarditis, osteomyelitis, and meningitis due to *Candida.*
- Treatment of Esophageal Candidiasis
- Treatment of Invasive Aspergillosis in patients who are refractory to or intolerant of other therapies.

IV. DOSAGE AND ADMINISTRATION

General Recommendations in Adult Patients

CANCIDAS should be administered in adults (≥ 18 years of age) by slow intravenous infusion over approximately 1 hour.

Empirical Therapy

A single 70-mg loading dose should be administered on Day 1, followed by 50 mg daily thereafter. Duration of treatment should be based on the patient's clinical response. Empirical therapy should be continued until up to 72 hours after resolution of neutropenia. Patients found to have a fungal infection should be treated for a minimum of 14 days; treatment should continue for at least 7 days after both neutropenia and clinical symptoms are resolved. If the 50-mg dose is well tolerated but does not provide an adequate clinical response, the daily dose can be increased to 70 mg. Although an increase in efficacy with 70 mg daily has not been demonstrated, safety data suggest that an increase in dose to 70 mg daily is well tolerated.

Candidemia and other Candida infections

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

Esophageal Candidiasis

Fifty (50) mg should be administered daily.

Invasive Aspergillosis

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

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 in adult patients with the metabolic inducers efavirenz, nevirapine, rifampicin, dexamethasone, phenytoin, or carbamazepine, use of a daily dose of 70 mg CANCIDAS should be considered.

Patients with Hepatic Insufficiency

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

Pediatric Patients

CANCIDAS should be administered in pediatric patients (12 months to 17 years of age) by slow IV infusion over approximately 1 hour. Dosing in pediatric patients (12 months to 17 years of age) should be based on the patient's body surface area (see section **INSTRUCTIONS FOR USE IN PEDIATRIC PATIENTS**, Mosteller[1] Formula). For all indications with the exception of esophageal candidiasis, a single 70-mg/m^2 loading dose (not to exceed an actual dose of 70 mg) should be administered on Day 1, followed by 50 mg/m^2 daily thereafter (not to exceed an actual dose of 70 mg daily). For the treatment of esophageal candidiasis, a dose of 50 mg/m^2 daily should be administered (not to exceed an actual dose of 70 mg daily). Duration of treatment should be individualized to the indication, as described for each indication in adults (see section **General Recommendations in Adult Patients**).

If the 50-mg/m^2 daily dose is well tolerated but does not provide an adequate clinical response, the daily dose can be increased to 70 mg/m^2 daily (not to exceed an actual daily dose of 70 mg). Although an increase in efficacy with 70 mg/m^2 daily has not been demonstrated, limited safety data suggest that an increase in dose to 70 mg/m^2 daily is well tolerated.

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

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[1] Mosteller RD: Simplified Calculation of Body Surface Area. N Engl J Med 1987 Oct 22;317(17): 1098 (letter)

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.

INSTRUCTIONS FOR USE IN ADULTS

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 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. The concentrations of the reconstituted vials will be: 7.2 mg/mL (70 mg vial) or 5.2 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 IN ADULTS

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	0.28 mg/mL	not recommended
70 mg (from two 50 mg vials)**	14 mL	0.28 mg/mL	not recommended
50 mg	10 mL	0.20 mg/mL	0.47 mg/mL
35 mg for moderate	5 mL	0.14 mg/mL	0.34 mg/mL

hepatic insufficiency (from one 70 mg vial)			
35 mg for moderate hepatic insufficiency (from one 50 mg vial)	7 mL	0.14 mg/mL	0.34 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

INSTRUCTIONS FOR USE IN PEDIATRIC PATIENTS

Calculation of Body Surface Area (BSA) for pediatric dosing

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

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

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

1. Determine the actual loading dose to be used in the pediatric patient by using the patient's BSA (as calculated above) and the following equation:

   BSA (m^2) X 70 mg/m^2 = Loading Dose

   The maximum loading dose on Day 1 should not exceed 70 mg regardless of the patient's calculated dose.
2. Equilibrate the refrigerated vial of CANCIDAS to room temperature.
3. Aseptically add 10.5 mL of 0.9% Sodium Chloride Injection, Sterile Water for Injection, Bacteriostatic Water for Injection with methylparaben and propylparaben, or Bacteriostatic Water for Injection with 0.9% benzyl alcohol.[a] This reconstituted solution may be stored for up to 24 hours at or below 25°C (≤ 77°F).[b] This will give a final caspofungin concentration in the vial of 7.2 mg/mL.
4. Remove the volume of drug equal to the calculated loading dose (Step 1) from the vial. Aseptically transfer this volume (mL)[c] of reconstituted CANCIDAS to an IV bag (or bottle) containing 250 mL of 0.9%, 0.45%, or 0.225% Sodium Chloride Injection, or Lactated Ringers Injection. Alternatively, the volume (mL)[c] of reconstituted CANCIDAS can be added to a reduced volume of 0.9%, 0.45%, or 0.225% Sodium Chloride Injection or Lactated Ringers Injection, not to exceed a final concentration of 0.5 mg/mL. This infusion solution must be used within 24 hours if stored at or below 25°C (≤ 77°F) or within 48 hours if stored refrigerated at 2 to 8°C (36 to 46°F).
5. If the calculated loading dose is <50 mg, then the dose may be prepared from the 50-mg vial [follow Steps 2-4 from *Preparation of the 50-mg/m² infusion for pediatric patients 12 months of age or older*

(using a 50-mg vial)]. The final caspofungin concentration in the 50-mg vial after reconstitution is 5.2 mg/mL.

Preparation of the 50-mg/m² infusion for pediatric patients 12 months of age or older (using a 50-mg vial)

1. Determine the daily maintenance dose to be used in the pediatric patient by using the patient's BSA (as calculated above) and the following equation:

   BSA (m^2) X 50 mg/m^2 = Daily Maintenance Dose

   The daily maintenance dose should not exceed 70 mg regardless of the patient's calculated dose.
2. Equilibrate the refrigerated vial of CANCIDAS to room temperature.
3. Aseptically add 10.5 mL of 0.9% Sodium Chloride Injection, Sterile Water for Injection, Bacteriostatic Water for Injection with methylparaben and propylparaben, or Bacteriostatic Water for Injection with 0.9% benzyl alcohol.[a] This reconstituted solution may be stored for up to 24 hours at or below 25°C (≤ 77°F).[b] This will give a final caspofungin concentration in the vial of 5.2 mg/mL.
4. Remove the volume of drug equal to the calculated loading dose (Step 1) from the vial. Aseptically transfer this volume (mL)[c] of reconstituted CANCIDAS to an IV bag (or bottle) containing 250 mL of 0.9%, 0.45%, or 0.225% Sodium Chloride Injection, or Lactated Ringers Injection. Alternatively, the volume (mL)[c] of reconstituted CANCIDAS can be added to a reduced volume of 0.9%, 0.45%, or 0.225% Sodium Chloride Injection or Lactated Ringers Injection, not to exceed a final concentration of 0.5 mg/mL. This infusion solution must be used within 24 hours if stored at or below 25°C (≤ 77°F) or within 48 hours if stored refrigerated at 2 to 8°C (36 to 46°F).
5. If the actual daily maintenance dose is >50 mg, then the dose may be prepared from the 70-mg vial [follow Steps 2-4 from *Preparation of the 70-mg/m² infusion for pediatric patients 12 months of age or older (using a 70-mg vial)*]. The final caspofungin concentration in the 70-mg vial after reconstitution is 7.2 mg/mL.

Preparation notes:

a. The white to off-white 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.

V. CONTRAINDICATIONS

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

VI. PRECAUTIONS

Anaphylaxis has been reported during administration of CANCIDAS. If this occurs, CANCIDAS should be discontinued and appropriate treatment administered. Possibly histamine-mediated adverse reactions, including rash, facial swelling, angioedema, pruritus, sensation of warmth, or bronchospasm have been reported and may require discontinuation and/or administration of appropriate treatment.

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported after post marketing use of caspofungin. Caution should apply in patients with history of allergic skin reactions.

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

Concomitant use of CANCIDAS with cyclosporine has been evaluated in adult healthy volunteers and in adult patients. Some healthy adult 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. In a retrospective study of 40 patients treated during marketed use with CANCIDAS and cyclosporine for 1 to 290 days (median 17.5 days), no serious hepatic adverse events were noted. As expected in patients with allogeneic hematopoietic stem cell transplants or solid organ transplants, hepatic enzyme abnormalities occurred commonly; however, no patient had elevations in ALT that were considered drug-related. Elevations in AST considered at least possibly related to therapy with CANCIDAS and/or cyclosporine occurred in 5 patients, but all were less than 3.6 times the ULN. Discontinuations due to laboratory abnormalities in hepatic enzymes from any cause occurred in 4 patients. Of these, 2 were considered possibly related to therapy with CANCIDAS and/or cyclosporine as well as other possible causes. In the prospective invasive aspergillosis and compassionate use studies, there were 6 adult patients treated with CANCIDAS and cyclosporine for 2 to 56 days; none of these patients experienced increases in hepatic enzymes. These data suggest that CANCIDAS can be used in patients receiving cyclosporine when the

potential benefit outweighs the potential risk. Close monitoring of liver enzymes should be considered if CANCIDAS and cyclosporine are used concomitantly.

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

VII. PREGNANCY

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.

VIII. NURSING MOTHERS

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

IX. PEDIATRIC USE

The safety and effectiveness of CANCIDAS in pediatric patients 12 months to 17 years of age are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in pediatric patients, and additional data from prospective studies in pediatric patients 12 months to 17 years of age for the following indications (see section III **INDICATIONS**):

- Empirical therapy for presumed fungal infections (such as *Candida* or *Aspergillus*) in febrile, neutropenic patients
- Treatment of Candidemia and the following *Candida* infections: intra-abdominal abscesses, peritonitis and pleural space infections. In the prospective pediatric study, the pediatric patient population studied with *Candida* intra-abdominal abscesses, peritonitis and pleural space infections was limited.
- Treatment of esophageal candidiasis. In the prospective pediatric study, the pediatric patient population studied with esophageal candidiasis was limited.
- Treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies

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

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

X. 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 who were treated empirically or who had invasive candidiasis, a similar modest effect of age was seen in older patients relative to younger patients. No dosage adjustment is necessary for elderly patients (65 years of age or more).

XI. 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.

In two adult clinical studies, cyclosporine (one 4 mg/kg dose or two 3 mg/kg doses) increased the AUC of caspofungin by approximately 35%. 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. In a retrospective study of 40 patients treated during marketed use with CANCIDAS and/or cyclosporine for 1 to 290 days (median 17.5 days), no serious hepatic adverse events were noted (see section VI **PRECAUTIONS**).

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

CANCIDAS reduced the 12-hour blood concentration (C_{12hr}) of tacrolimus (FK-506) by 26% in healthy adult volunteers. For patients receiving both therapies, standard monitoring of tacrolimus blood concentrations and appropriate tacrolimus dosage adjustments are recommended.

Results from two clinical drug interaction studies in healthy adult volunteers indicate that rifampicin both induces and inhibits caspofungin disposition with net induction at steady state. In one study, rifampicin and caspofungin were co-administered for 14 days with both therapies initiated on the same day. In the second study, rifampicin was administered alone for 14 days to allow the induction effect to reach steady state, and then rifampicin and caspofungin were co-administered for an additional 14 days. When the induction effect of rifampicin 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 rifampicin was demonstrated when rifampicin 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 rifampicin therapy, and no elevation in caspofungin concentrations occurred. In addition, results from population pharmacokinetic screening in adults 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 to adult patients with inducers of drug clearance, such as efavirenz, nevirapine, rifampicin, dexamethasone, phenytoin, or carbamazepine, use of a daily dose of 70 mg of CANCIDAS should be considered (see section IV **DOSAGE AND ADMINISTRATION**).

In pediatric patients, results from regression analyses of pharmacokinetic data suggest that co-administration of dexamethasone with CANCIDAS may result in clinically meaningful reductions in caspofungin trough concentrations. This finding may indicate that pediatric patients will have similar reductions with inducers as seen in adults. When CANCIDAS is co-administered to pediatric patients with inducers of drug clearance, such as rifampin, efavirenz, nevirapine, phenytoin, dexamethasone, or carbamazepine, a CANCIDAS dose of 70-mg/m^2 daily (not to exceed an actual daily dose of 70 mg) should be considered.

XII. SIDE EFFECTS

Hypersensitivity reactions have been reported (see section VI. **PRECAUTIONS**).

Adult Patients

In clinical studies, 1865 adult individuals received single or multiple doses of CANCIDAS: 564 febrile, neutropenic patients (empirical therapy study), 382 patients with invasive candidiasis, 297 patients with esophageal and/or oropharyngeal candidiasis, 228 patients with invasive aspergillosis and 394 individuals in phase I studies. In the empirical therapy study patients had received chemotherapy for malignancy or had undergone hematopoietic stem-cell transplantation. In the studies involving patients with documented *Candida* infections, the majority of the patients had serious underlying medical conditions (e.g., hematologic

or other malignancy, recent major surgery, HIV) 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.

Phlebitis was a commonly reported local injection-site adverse reaction in all patient populations.
Other local reactions included erythema, pain/tenderness, itching, discharge, and a burning sensation.

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

The following adverse reactions were reported:

[Very common (≥ 1/10), Common (≥ 1/100, <1/10), Uncommon (>1/1,000, <1/100)]

Blood and lymphatic system disorders:
Common: haemoglobin decreased, haematocrit decreased, white blood cell count decreased
Uncommon: anaemia, thrombocytopaenia, coagulopathy, leukopaenia, eosinophil count increased, platelet count decreased, platelet count increased, lymphocyte count decreased, white blood cell count increased, neutrophil count decreased

Metabolism and nutrition disorders:
Common: hypokalemia
Uncommon: fluid overload, hypomagnesaemia, anorexia, electrolyte imbalance, hyperglycaemia, hypocalcaemia, metabolic acidosis

Psychiatric disorders
Uncommon: anxiety, disorientation, insomnia

Nervous system disorders:
Common: headache
Uncommon: dizziness, dysgeusia, paraesthesia, somnolence, tremor, hypoaesthesia

Eye disorders:
Uncommon: ocular icterus, vision blurred, eyelid oedema, lacrimation increased

Cardiac disorders:
Uncommon: palpitations, tachycardia, arrhythmia, atrial fibrillation, cardiac failure congestive

Vascular disorders:

Common: phlebitis

Uncommon: thrombophlebitis, flushing, hot flush, hypertension, hypotension

Respiratory, thoracic and mediastinal disorders:

Common: dyspnoea

Uncommon: nasal congestion, pharyngolaryngeal pain, tachypnoea, bronchospasm, cough, dyspnoea paroxysmal nocturnal, hypoxia, rales, wheezing

Gastrointestinal disorders:

Common: nausea, diarrhoea, vomiting

Uncommon: abdominal pain, abdominal pain upper, dry mouth, dyspepsia, stomach discomfort, abdominal distension, ascites, constipation, dysphagia, flatulence

Hepatobiliary disorders:

Common: elevated liver values (alanine aminotransferase, aspartate aminotransferase, blood alkaline phosphatase, bilirubin conjugated, blood bilirubin)

Uncommon: cholestasis, hepatomegaly, hyperbilirubinaemia, jaundice, hepatic function abnormal, hepatotoxicity, liver disorder

Skin and subcutaneous tissue disorders:

Common: rash, pruritus, erythema, hyperhidrosis

Uncommon: erythema multiforme, rash macular, rash maculo-papular, rash pruritic, urticaria, dermatitis allergic, pruritus generalised, rash erythematous, rash generalised, rash morbilliform, skin lesion

Musculoskeletal and connective tissue disorders

Common: arthralgia

Uncommon: back pain, pain in extremity, bone pain, muscular weakness, myalgia

Renal and urinary disorders

Uncommon: renal failure, renal failure acute

General disorders and administration site conditions:

Common: pyrexia, chills, infusion-site pruritus

Uncommon: pain, catheter site pain, fatigue, feeling cold, feeling hot, infusion site erythema, infusion site induration, infusion site pain, infusion site swelling, injection site phlebitis, oedema peripheral, tenderness, chest discomfort, chest pain, face oedema, feeling of body temperature change, induration, infusion site extravasation, infusion site irritation, infusion site phlebitis, infusion site rash, infusion site urticaria, injection site erythema, injection site oedema, injection site pain, injection site swelling, malaise, oedema

Investigations:

Common: blood potassium decreased, blood albumin decreased

Uncommon: blood creatinine increased, red blood cells urine positive, protein total decreased, protein urine present, prothrombin time prolonged, prothrombin time shortened, blood sodium decreased, blood sodium increased, blood calcium decreased, blood calcium increased, blood chloride decreased, blood glucose increased, blood magnesium decreased, blood phosphorus decreased, blood phosphorus increased, blood urea increased, gamma-glutamyltransferase increased, activated partial thromboplastin time prolonged, blood bicarbonate decreased, blood chloride increased, blood potassium increased, blood pressure increased, blood uric acid decreased, blood urine present, breath sounds abnormal, carbon dioxide decreased, immunosuppressant drug level increased, international normalised ratio increased, urinary casts, white blood cells urine positive, and pH urine increased.

Also reported in patients with invasive aspergillosis were pulmonary oedema, adult respiratory distress syndrome (ARDS), and radiographic infiltrates.

Pediatric Patients

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

The following adverse reactions were reported:

[Very common (≥ 1/10), Common (≥ 1/100, <1/10)]

Blood and lymphatic system disorders:

Common: eosinophil count increased

Nervous system disorders:

Common: headache

Cardiac disorders:

Common: tachycardia

Vascular disorders:

Common: flushing, hypotension

Hepatobiliary disorders:

Common: elevated liver enzyme levels (AST, ALT)

Skin and subcutaneous tissue disorders:

Common: rash, pruritus

General disorders and administration site conditions:

Very common: fever

Common: chills, catheter site pain

Investigations:

Common: decreased potassium, hypomagnesemia, increased glucose, decreased phosphorus, and increased phosphorus

Post-marketing experience:

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

Gastrointestinal disorders: pancreatitis

Hepatobiliary: rare cases of hepatic dysfunction

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

Renal and urinary disorders: clinically significant renal dysfunction

Laboratory abnormalities: hypercalcemia, gamma-glutamyltransferase increased

General disorders and administration site condition: swelling and peripheral edema

XIII. OVERDOSAGE

Inadvertent administration of up to 400 mg of caspofungin in one day has been reported. These occurrences did not result in clinically important adverse experiences. Caspofungin is not dialyzable.

XIV. AVAILABILITY

CANCIDAS 50 mg/vial, CANCIDAS 70 mg/vial

XV. 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 up to 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 up to 24 hours, or for up to 48 hours when refrigerated at 2 to 8°C (36 to 46°F).

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