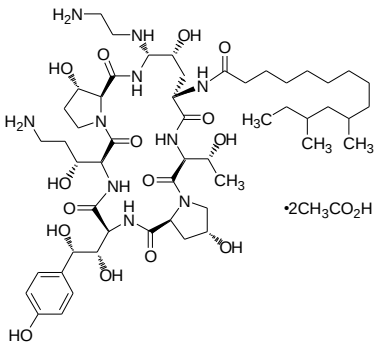
PRODUCT INFORMATION

CANCIDAS ®
(caspofungin acetate)

DESCRIPTION

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

CANCIDAS (caspofungin acetate) is 1-[(4*R*,5*S*)-5-[(2-aminoethyl)amino]-*N*^{2}-(10,12-dimethyl-1-oxotetradecyl)-4-hydroxy-*L*-ornithine]-5-[(3*R*)-3-hydroxy-*L*-ornithine]pneumocandin B_0 diacetate (salt). In addition to the active ingredient caspofungin acetate, CANCIDAS contains the following inactive ingredients: sucrose, mannitol, acetic acid, glacial, and sodium hydroxide. Caspofungin acetate is a hygroscopic, white to off-white powder. It is freely soluble in water and methanol, and slightly soluble in ethanol. The pH of a saturated aqueous solution of caspofungin acetate is approximately 6.6. The empirical formula is $C_{52}H_{88}N_{10}O_{15}$•$2C_2H_4O_2$ and the formula weight is 1213.42. The CAS No is 179463-17-3. The structural formula is:



PHARMACOLOGY

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.

Microbiology

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*)
Candida species (including *Candida albicans, Candida dublinensis*, *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*, † (μg/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.

Standardised techniques for susceptibility testing have been established for yeasts by EUCAST. No standardised 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. Caspofungin has been reported to be active in the prevention and treatment of pulmonary aspergillosis in a rat model.

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 μg/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 μg/mL for growth inhibition have developed in a mouse model of *C. albicans* infection. Isolates of *Candida* with reduced susceptibility to caspofungin have been identified in a small number of patients during treatment (MICs for caspofungin >2 μg/mL using standardised 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.

Development of *in vitro* resistance to caspofungin by *Aspergillus* species has been identified. 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.

Pharmacokinetics

Absorption

Absorption is not relevant since caspofungin acetate is administered intravenously.

Distribution

Plasma concentrations of caspofungin decline in a polyphasic manner following single 1-hour IV infusions. A short α-phase occurs immediately post-infusion, followed by a β-phase (half-life of 9 to 11 hours) that characterises much of the profile and exhibits clear log-linear behaviour from 6 to 48 hours post-dose (during which the plasma concentration decreases by an order of magnitude). An additional, longer half-life (γ-) phase, also occurs with a half-life of 40-50 hours.

Distribution, rather than excretion or biotransformation, is the dominant mechanism influencing plasma clearance. Caspofungin is extensively bound to albumin (~97%), and distribution into red blood cells is minimal. Mass balance results showed that approximately 92% of the [^{3}H] label was found in tissues 36 to 48 hours after a single 70 mg dose of [^{3}H] caspofungin acetate. There is little excretion or biotransformation of caspofungin during the first 30 hours after administration.

Metabolism

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

Excretion

Two single-dose radiolabelled pharmacokinetic studies were conducted. In one study, plasma, urine, and faeces were collected over 27 days, and in the second study, plasma was collected over six months. Approximately 75% of the radioactivity was recovered: 41% in urine and 34% in faeces. Plasma concentrations of radioactivity and of caspofungin were similar during the first 24 to 48 hours post-dose; thereafter drug levels fell more rapidly. In plasma, caspofungin concentrations fell below the limit of quantitation after 6 to 8 days post-dose, while radio-label fell

below the limit of quantitation at 22.3 weeks post-dose. A small amount of caspofungin is excreted unchanged in urine (~1.4% of dose). Renal clearance of parent drug is low (~0.15 mL/min).

Special Populations

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 area under the curve (AUC) for caspofungin was elevated slightly (approximately 20%) in women relative to men. No dosage adjustment is necessary based on gender.

Geriatric

Plasma concentrations of caspofungin in healthy older men and women (≥65 years of age) were increased slightly (approximately 28% in area under the curve [AUC]) compared to young healthy men. In patients who were treated empirically or who had invasive candidiasis, a similar modest effect of age was seen in older patients relative to younger patients. No dosage adjustment is necessary for the elderly.

Race

No clinically significant differences in the pharmacokinetics of caspofungin were seen among Caucasians, Blacks, Hispanics, and persons of mixed race. No dosage adjustment is necessary on the basis of race.

Renal Insufficiency

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

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 (21 to 26% in AUC) on Days 7 and 14 relative to healthy control subjects. No dosage adjustment is recommended for patients with mild hepatic insufficiency. Patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9) who received a single 70 mg dose of CANCIDAS had an average plasma caspofungin increase of 76% compared to control subjects.

A dosage reduction is recommended for patients with moderate hepatic insufficiency (see DOSAGE AND ADMINISTRATION). There is no clinical experience in patients with severe hepatic insufficiency (Child-Pugh score >9).

Paediatric Patients

CANCIDAS has been studied in five prospective studies involving paediatric patients under 18 years of age, including three paediatric 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).
- In young children and toddlers (ages 3 to 23 months) receiving caspofungin at 50 mg/m^2 daily (maximum 70 mg daily), the caspofungin plasma $AUC_{0\text{-}24hr}$ after multiple doses was comparable to that seen in adults receiving caspofungin at 50 mg daily. As in the older children, these young children who received 50 mg/m^2 daily had slightly higher $AUC_{0\text{-}24\ hr}$ values on Day 1 relative to adults receiving the standard 50-mg daily dose. The caspofungin pharmacokinetic results from the young children (3 to 23 months of age) that received 50 mg/m^2 caspofungin daily were similar to the pharmacokinetic results from older children (2 to 11 years of age) that received the same dosing regimen.
- In neonates and infants (<3 months) receiving caspofungin at 25 mg/m^2 daily, caspofungin peak concentration ($C_{1\ hr}$) and caspofungin trough concentration ($C_{24\ hr}$) after multiple doses were comparable to that seen in adults receiving caspofungin at 50 mg daily. On Day 1, $C_{1\ hr}$ was comparable and $C_{24\ hr}$ 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 has not been adequately studied in prospective clinical trials involving neonates and infants under 3 months of age.

Based on population pharmacokinetic analyses including data from the 2 efficacy studies in paediatric population and in comparison with healthy adults and adult patients, the caspofungin $C_{1\ hr}$ was significantly increased (50 – 163%) in paediatric patients of all age groups, whereas $C_{24\ hr}$ was significantly increased (25-109%) in older children (2 – 11 years) and adolescents (12 – 17 years), but was similar to adults in young children (3 – 24 months). The estimated increase in $AUC_{0\text{-}24}$ hr was 38 – 41% in paediatric patients of all age groups compared with adult patients.

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.

Clinical Trials

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

Empirical Therapy in febrile, neutropenic patients

A multicentre, double-blind study enrolled 1111 febrile, neutropenic, adult patients (mean age 48 years, range 16-83; 56% male) who were randomised to treatment with daily doses of CANCIDAS (50 mg/day following a 70 mg loading dose on Day 1) or AmBisome®[1] (liposomal amphotericin for injection, 3.0 mg/kg/day). Eligible patients had received chemotherapy for malignancy or had undergone haematopoietic stem-cell transplantation (HSCT), and presented with neutropenia (<500 cells/mm^3 for 96 hours) and fever (>38.0°C) that had not responded to antibacterial therapy. Any patient known to have a documented fungal infection was excluded from entering the study. Patients were to be treated until resolution of neutropenia, with a maximum treatment duration of 28 days. However, patients found to have a documented fungal infection could be treated longer. If the drug was well tolerated but the patient's fever persisted and clinical condition deteriorated following 5 days of therapy, the dosage of study drug could be increased to 70 mg/day for CANCIDAS (13.3% of patients treated) or to 5.0 mg/kg/day for AmBisome (14.3% of patients treated).

Patients were stratified based on risk category [high-risk patients had undergone allogeneic HSCT (7.0% total) or had relapsed acute leukaemia (17.7% total)] and on receipt of prior antifungal prophylaxis. The percentage of patients in the high-risk stratum at entry was 26.6% for the CANCIDAS group and 22.9% for the AmBisome group. In both groups a similar percentage of patients had received antifungal prophylaxis. The most frequent diagnoses were acute myelogenous leukaemia, acute lymphocytic leukaemia, and non-Hodgkin's lymphoma.

Patients who met the entry criteria and received at least one dose of study therapy were included in the modified intention-to-treat (MITT) population (556 treated with CANCIDAS and 539 treated with AmBisome). The mean duration of study therapy was 13 days. An overall favourable response required meeting each of 5 criteria: 1) successful treatment of any baseline fungal infection, 2) no breakthrough fungal infections during administration of study drug or within 7 days after completion of treatment, 3) survival for 7 days after completion of study therapy, 4) no discontinuation of the study drug because of drug-related toxicity or lack of efficacy, and 5) resolution of fever during the period of neutropenia.

An independent expert panel adjudicated blinded data from all patients identified as having a suspected invasive fungal infection. The panel assessed the presence of invasive fungal infection, timing of onset (baseline or breakthrough), causative pathogen, and, for baseline infections, response to study treatment. The only fungal infections considered to be present for purposes of statistical analysis were those classified by the expert panel as either probable or proven. Approximately 5% of patients were found to have baseline fungal infections, of which the majority were due to *Aspergillus* or *Candida* species.

The proportion of MITT patients with an overall favourable response and the proportion of MITT patients with favourable responses to the individual criteria are shown in Table 2.

[1] Registered trademark of Gilead Sciences, Inc.

Table 2

Favourable Response of Patients with Persistent Fever and Neutropenia

	CANCIDAS*	AmBisome*	% Difference (Confidence Interval) **
Number of Patients (Modified Intention-To-Treat)	556	539	
Overall Favourable Response	190 (33.9%)	181 (33.7%)	0.2 (-5.6, 6.0)
1. Successful treatment of any baseline fungal infection	14/27 (51.9%)	7/27 (25.9%)	25.9 (0.9, 51.0)†
2. No breakthrough fungal infection	527 (94.8%)	515 (95.5%)	-0.8 (-3.3, 1.8)
3. Survival 7 days after end of treatment	515 (92.6%)	481 (89.2%)	3.4 (0.0, 6.8)
4. No discontinuation due to toxicity or lack of efficacy	499 (89.7%)	461 (85.5%)	4.2 (0.3, 8.1)†
5. Resolution of fever during neutropenia	229 (41.2%)	223 (41.4%)	-0.2 (-6.0, 5.6)

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

** Overall Response (primary efficacy endpoint): estimated % difference adjusted for strata and expressed as CANCIDAS – AmBisome (95.2% CI);, based on all 5 criteria
Individual Criteria: % difference calculated as CANCIDAS – AmBisome (95% CI).

† Statistically significant difference.

Based on overall favourable response rates, CANCIDAS was as effective as AmBisome in empirical therapy of persistent febrile neutropenia. CANCIDAS had significantly higher favourable response rates than AmBisome for the following criteria: successful treatment of any baseline fungal infection (CANCIDAS 51.9%, AmBisome 25.9%) and absence of premature discontinuation from study therapy due to toxicity or lack of efficacy (CANCIDAS 89.7%, AmBisome 85.5%). CANCIDAS was comparable to AmBisome for the other criteria (absence of a breakthrough fungal infection, survival for 7 days after the end of treatment, and resolution of fever during neutropenia).

Overall favourable response rates were comparable in high-risk patients (CANCIDAS 43.2%, AmBisome 37.7%) and low-risk patients (CANCIDAS 31.0%, AmBisome 32.4%). Rates were also comparable in patients who had received prior antifungal prophylaxis (CANCIDAS 33.5%, AmBisome 32.9%) and those who had not (CANCIDAS 35.0%, AmBisome 34.5%).

The majority of baseline infections were due to *Aspergillus* or *Candida* species. Response rates to CANCIDAS and AmBisome for baseline infections caused by *Aspergillus* species were, respectively, 41.7% (5/12) and 8.3% (1/12), and by *Candida* species were 66.7% (8/12) and 41.7% (5/12).

Invasive Candidiasis

In an initial Phase III randomised, 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 favourable 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 (candidaemia) (83%) and *Candida* peritonitis (10%), patients with *Candida* endocarditis, osteomyelitis or meningitis were excluded from this study. Most infections were caused by *C. albicans* (45%), followed by *C. parapsilosis* (19%), *C. tropicalis* (16%), *C. glabrata* (11%), and *C. krusei* (2%). The favourable response rates at the end of IV study therapy are shown in Table 3.

Table 3
Favourable Response Rates to IV Study Therapy
Among Patients with Invasive Candidiasis (and Candidaemia)

	CANCIDAS 50 mg* % (n/m**) [95% CI]	Amphotericin B % (n/m) [95% CI]	Difference (%) after Adjusting for strata [95.6% CI]
ALL PATIENTS WITH INVASIVE CANDIDIASIS			
MITT analysis	73.4% (80/109) [65.1, 81.7]	61.7% (71/115) [52.8, 70.7]	12.7% [-0.7, 26.0]
Neutropenic patients (ANC ≤ 500μL)	50% (7/14)	40% (4/10)	
APACHE II scores >20 at study entry	57.1% (12/21)	43.5% (10/23)	
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 WITH CANDIDAEMIA			
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 favourable response at the end of IV study therapy/number of patients included in analysis

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, with an overall mortality among MITT patients during the study treatment period and 6 to 8-week follow-up period of 33.0% in the CANCIDAS group and 30.4% in the amphotericin B group.

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.

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 candidaemia. 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 favourable response rates at the end of IV study therapy for patients with candidaemia are shown in Table 3.

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

In a second Phase III randomised, double-blind study, patients with a proven diagnosis of invasive candidiasis received daily doses of CANCIDAS 50 mg/day (following a 70-mg loading dose on Day 1) or CANCIDAS 150 mg/day. The diagnostic criteria, efficacy time points, and efficacy endpoints used in this study were similar to those employed in the prior study. Efficacy was a secondary endpoint in this study. Patients who met the entry criteria and received one or more doses of caspofungin study therapy were included in the efficacy analysis. The favorable overall response rates at the end of CANCIDAS therapy were similar in the 2 treatment groups: 72% (73/102) and 78% (74/95) for the CANCIDAS 50-mg and 150-mg treatment groups, respectively (difference 6.3% [95% CI -5.9, 18.4]).

Oesophageal Candidiasis

A total of 393 patients with oesophageal candidiasis were enrolled in three comparative studies to evaluate the efficacy of CANCIDAS for the treatment of oesophageal candidiasis. Patients were required to have symptoms and microbiological documentation of oesophageal candidiasis; and most patients were significantly immunocompromised. Disease severity was determined by oesophagoscopy (endoscopy).

In the randomised, double-blind study comparing CANCIDAS 50 mg/day (n=83) versus IV fluconazole 200 mg/day (n=94) for the treatment of oesophageal candidiasis, patients were treated for 7 to 21 days. A favourable overall response required both complete resolution of symptoms and significant endoscopic improvement 5 to 7 days following discontinuation of study therapy. The definition of endoscopic response was based on severity of disease at baseline using a 4 grade scale and required at least a two grade reduction from baseline endoscopic score or reduction to grade 0 for patients with a baseline score of 2 or less. The proportion of patients with a favourable response to CANCIDAS was comparable to that seen with fluconazole, as demonstrated in Table 4.

Table 4
Oesophageal Candidiasis study: CANCIDAS v fluconazole
Proportion of patients with a favourable response

	CANCIDAS 50 mg n/m (%) [95% Confidence Interval]	Fluconazole 200 mg n/m (%) [95% Confidence Interval]	Observed Difference (%) [95% Confidence Interval]
Favourable Overall Combined Response (Symptoms and Endoscopy	66/81 (81.5) [71.3, 89.2]	80/94 (85.1) [76.3, 91.6]	-3.6 [-14.7, 7.5]
Symptom Response	73/81 (90.1) [81.5, 95.6]	84/94 (89.4) [81.3, 94.8]	0.8 [-8.2, 9.8]
Endoscopy Response	69/81 (85.2) [75.6, 92.1]	81/94 (86.2) [77.5, 92.4]	-1.0 [-11.4, 9.4]

*n/m=number of patients with a favourable assessment/patients with data at 5 to 7 day follow-up visit

In addition, 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). These clinical studies support the use of CANCIDAS 50 mg daily in the treatment of oesophageal candidiasis. Increasing doses of CANCIDAS above 50 mg daily provided no additional benefit in the treatment of oesophageal candidiasis.

Invasive Aspergillosis

Sixty nine patients between the ages of 18 and 80 with invasive aspergillosis were enrolled in an open-label, non-comparative study to evaluate the safety, tolerability, and efficacy of CANCIDAS. Enrolled patients had previously been refractory to or intolerant of other antifungal therapy. Refractory patients were classified as those who had disease progression or failed to improve despite therapy for at least 7 days with amphotericin B, lipid formulations of amphotericin B, itraconazole, or an investigational azole (voriconazole) with reported activity against *Aspergillus*. Intolerance to previous therapy was defined as a doubling of creatinine (or creatinine $\geq$ 2.5 mg/dL while on therapy), other acute reactions, or infusion-related toxicity.

To be included in the study, patients with pulmonary disease must have had definite (positive tissue histopathology or positive culture from tissue obtained by an invasive procedure) or probable (positive radiographic or computed tomographic evidence with supporting culture from bronchoalveolar lavage or sputum, galactomannan enzyme-linked immunosorbent assay, and/or polymerase chain reaction) invasive aspergillosis.

Patients with extrapulmonary disease had to have definite invasive aspergillosis. The definitions were modelled after the Mycoses Study Group Criteria. 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 favourable 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 unfavourable response.

Among the 69 patients enrolled in the study, 63 met entry diagnostic criteria and had outcome data; and of these, 52 patients received treatment for >7 days. Fifty-three (84%) were refractory to previous antifungal therapy and 10 (16%) were intolerant. Forty five patients had pulmonary disease and 18 had extrapulmonary disease. Underlying conditions were haematologic malignancy (N=24), allogeneic bone marrow transplant or stem cell transplant (N=18), organ transplant (N=8), solid tumour (N=3), or other conditions (N=10). Fourteen patients were neutropenic (ANC < 500/μL) at baseline; two of these patients had a favourable response to caspofungin therapy and evidence of their clinical response was seen prior to recovery of their neutrophil counts. In addition, 3 patients who had become neutropenic during caspofungin therapy all had a favourable response. None of the 7 patients who were persistently neutropenic had a favourable response.

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); 5 of these 18 patients had a favourable response. Among the 23 patients receiving high-dose corticosteroids, 8 had a favourable response, including 5 who continued on high-dose steroids. Overall, the expert panel determined that 41% (26/63) of patients receiving at least one dose of CANCIDAS had a favourable response. For those patients who received >7 days of therapy with CANCIDAS, 50% (26/52) had a favourable response. The favourable response rates for patients who were either refractory to or intolerant of previous therapies were 36% (19/53) and 70% (7/10), respectively. The response rates among patients with pulmonary disease and extrapulmonary disease were 47% (21/45) and 28% (5/18), respectively. Among patients with extrapulmonary disease, 2 of 8 patients who also had definite, probable, or possible CNS involvement had a favourable response.

A medical chart review of 206 patients with invasive aspergillosis was also conducted to assess the response to standard (non-investigational) therapies. Patient characteristics and important risk factors in this review were similar to those of patients enrolled in the open-label non-comparative 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 favourable response rate from this historical control study was 17% (35/206) for standard therapy compared to the favourable response rate of 41% (26/63) for CANCIDAS in the open-label non-comparative study (the odds ratio was approximately 3).

Paediatric Patients

The safety and efficacy of CANCIDAS was evaluated in paediatric patients 3 months to 17 years of age in two prospective, multicentre clinical trials.

The first study, which enrolled 82 patients between 2 to 17 years of age, was a randomised, double-blind study comparing CANCIDAS (50 mg/m^2 IV once daily following a 70-mg/m^2 loading dose on Day 1 [not to exceed 70 mg daily]) to AmBisome (3 mg/kg IV daily) in a 2:1 treatment fashion (56 on caspofungin, 26 on AmBisome) as empirical therapy in paediatric patients with persistent fever and neutropenia. The study design and criteria for efficacy assessment were similar to the study in adult patients (*see Clinical Trials, Empirical Therapy in febrile, neutropenic patients*). Patients were stratified based on risk category (high-risk patients had undergone allogeneic stem cell transplantation or had relapsed acute

leukaemia). Twenty-seven percent of patients in both treatment groups were high risk. The overall success rates in the MITT analysis, adjusted for strata, were as follows: 46% (26/56) for CANCIDAS and 32% (8/25) for AmBisome. For those patients in the high risk category, the favourable overall response rate was 60% (9/15) in the CANCIDAS group and 0% (0/7) in the AmBisome group.

The second study was a prospective, open-label, non-comparative study estimating the safety and efficacy of caspofungin in paediatric patients (ages 3 months to 17 years) with invasive candidiasis, oesophageal candidiasis, and invasive aspergillosis (as salvage therapy). The study employed diagnostic criteria which were based on established EORTC/MSG criteria of proven or probable infection; these criteria were similar to those criteria employed in the adult studies for these various indications. Similarly, the efficacy time points and endpoints used in this study were similar to those employed in the corresponding adult studies (*see Clinical Trials, Invasive Candidiasis, Candidaemia, Oesophageal Candidiasis, Invasive Aspergillosis*). All patients received CANCIDAS at 50 mg/m^2 IV once daily following a 70-mg/m^2 loading dose on Day 1 (not to exceed 70 mg daily). Among the 49 enrolled patients who received CANCIDAS, 48 were included in the MITT analysis. Of these 48 patients, 37 had invasive candidiasis, 10 had invasive aspergillosis, and 1 patient had oesophageal candidiasis. The favourable response rate, by indication, at the end of caspofungin therapy was as follows in the MITT analysis: 81% (30/37) in invasive candidiasis, 50% (5/10) in invasive aspergillosis, and 100% (1/1) in oesophageal candidiasis.

INDICATIONS

CANCIDAS is indicated for:

- Empirical therapy for presumed fungal infections in febrile, neutropenic patients whose fever has failed to respond to broad-spectrum antibiotics

- Treatment of:
  - -Invasive Candidiasis, including candidaemia
  - -Oesophageal Candidiasis
  - -Invasive Aspergillosis in patients who are refractory to or intolerant of other therapies.

CONTRAINDICATIONS

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

PRECAUTIONS

General

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.

Safety information on treatment durations longer than 4 weeks is limited, however available data suggest that CANCIDAS continues to be well tolerated with longer courses of therapy.

Laboratory abnormalities in liver function tests have been seen in healthy volunteers and in adult and paediatric patients treated with CANCIDAS. In some adult and paediatric 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.

Carcinogenesis / Mutagenesis / Impairment of Fertility

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

Caspofungin did not show evidence of genotoxic potential when evaluated in assays for gene mutation [bacterial (Ames) and mammalian cell (V79 Chinese hamster lung fibroblasts) assays] and chromosomal damage (Chinese hamster ovary cells *in vitro* and the mouse bone marrow chromosomal assay). Caspofungin was also negative in the alkaline elution/rat hepatocytes DNA strand break test.

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

Use in Pregnancy (Category B3)

CANCIDAS was shown to be weakly embryotoxic in rats and rabbits. In rats, CANCIDAS was shown to cause the complete ossification of the skull and torso and an increased incidence of cervical rib. Caspofungin also produced increases in resorptions in rats and rabbits and pre-implantation losses in rats. These findings were observed at doses that produced drug exposures similar to those seen in patients treated with a 70 mg dose (1-2 fold clinical exposure at the maximum recommended dose, based on AUC). Caspofungin crossed the placental barrier in rats and rabbits and was detected in the plasma of foetuses of pregnant animals dosed with CANCIDAS. There were 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 foetus.

Use in Lactation

Caspofungin was found in the milk of lactating, drug-treated rats. It is not known whether caspofungin is excreted in human milk. Because many drugs are excreted in human milk, women receiving CANCIDAS should not breast-feed.

Use in children

The use of caspofungin in paediatric patients 3 months to 17 years of age is supported by efficacy/safety studies in adults, pharmacokinetic studies in paediatric patients (see Pharmacokinetics subsection) and two prospective efficacy studies in

paediatric patients (see Clinical Trials section).

The efficacy and safety of caspofungin has not been studied in prospective clinical trials involving neonates and infants under 3 months of age.

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

The pharmacokinetic, efficacy, and safety data for patients aged 3 to 12 months of age are limited. Caution is advised when treating this age group.

Interactions with Other Drugs

Table 5

Co-administered drug	**CANCIDAS dose**	**N**	**Results**
Cyclosporin A 4 mg/kg as a single dose	70 mg daily for 11 days	19	Approximately 35% increase in CANCIDAS AUC when co-administered with Cyclosporin A*; no effect of CANCIDAS on cyclosporin A
Amphotericin B 0.25 mg/kg as a single dose	50 mg daily for 11 days	21	No effect of Amphotericin B on CANCIDAS; no effect of CANCIDAS on Amphotericin B
Itraconazole 200mg/d, multiple doses	50 mg daily for 14 days	47	No effect of itraconazole on CANCIDAS; no effect of CANCIDAS on itraconazole
Mycophenolate 1.5g as a single dose	50 mg daily for 16 days	18	No effect of mycophenolate on CANCIDAS; no effect of CANCIDAS on mycophenolate
Tacrolimus 0.1 mg/kg, doses on days 1 and 10	70 mg or 50 mg daily	51	No effect of tacrolimus on CANCIDAS; 20% decrease in AUC for tacrolimus when co-administered with CANCIDAS.
Rifampicin 600 mg oral dose daily When CANCIDAS added to pre-existing rifampicin (i.e. steady state) therapy When CANCIDAS and rifampicin initiated on the same day	50 mg daily for 14 days (for both studies)	14 10	Approximately 30 % decrease in trough concentrations of CANCIDAS, but with little change in AUC for CANCIDAS. No effect of CANCIDAS on rifampicin. Approximately 60% increase in AUC for CANCIDAS on Day 1. No effect of CANCIDAS on rifampicin. Refer to Dosage and Administration section
Nelfinavir 1250 mg oral dose twice daily	50 mg daily for 14 days	9	No effect of nelfinavir on CANCIDAS.

*Refer below for trial description

Cyclosporin

Concomitant use of CANCIDAS with cyclosporin has been evaluated in healthy adult volunteers and in adult patients. In one clinical study, 3 of 4 healthy adult subjects who received CANCIDAS 70 mg on Days 1 through 10, and also received two 3 mg/kg doses of cyclosporin 12 hours apart on Day 10, developed transient elevations of alanine transaminase (ALT) on Day 11 that were 2 to 3 times the upper limit of

normal (ULN). In a separate panel of adult subjects in the same study, 2 of 8 who received CANCIDAS 35 mg daily for 3 days and cyclosporin (two 3 mg/kg doses administered 12 hours apart) on Day 1 had small increases in ALT (slightly above the ULN) on Day 2. In both groups, elevations in aspartate transaminase (AST) paralleled ALT elevations, but were of lesser magnitude (see ADVERSE REACTIONS, *Laboratory Abnormalities*).

In the above two clinical studies, cyclosporin 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 cyclosporin. Refer to Table 5.

A retrospective study was conducted of 40 adult patients treated during marketed use with CANCIDAS and cyclosporin for 1 to 290 days (median 17.5 days). The majority of patients had allogeneic haematopoietic stem cell transplants (82.5%) or solid organ transplants (10%). The majority of patients received caspofungin 50 mg daily after 70 mg on Day 1. No serious hepatic adverse events were noted during this study. As expected in this population, 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 cyclosporin 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 cyclosporin as well as other possible causes. In the prospective invasive aspergillosis and compassionate use studies, there were 6 patients treated with CANCIDAS and cyclosporin 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 cyclosporin when the potential benefit outweighs the potential risk.

Tacrolimus

Clinical studies in healthy adult volunteers show that the pharmacokinetics of CANCIDAS are not altered by tacrolimus. CANCIDAS reduced the blood AUC of tacrolimus by approximately 20%, maximal blood concentration (C_{max}) by 16%, and 12-hour blood concentration (C_{12hr}) by 26% in healthy 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. Refer to Table 5.

Effect of caspofungin on the P450 (CYP) system

Studies *in vitro* show that caspofungin is not an inhibitor of cytochrome P450 (CYP) mediated reactions. In clinical studies, caspofungin did not induce the CYP3A4 metabolism of other drugs. Caspofungin is not a substrate for P-glycoprotein, and metabolism by cytochrome P450 was not observed *in vitro*.

Other Drugs

Clinical studies in healthy adult volunteers show that the pharmacokinetics of CANCIDAS are not altered by itraconazole, amphotericin B, nelfinavir or mycophenolate. CANCIDAS has no effect on the pharmacokinetics of itraconazole, amphotericin B, rifampicin or the active metabolite of mycophenolate. Refer to Table 5.

Population pharmacokinetic screening of caspofungin concentrations in adult 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 cyclosporin, are uncommon. Results from two clinical drug interaction studies 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 pre-existing rifampicin therapy, and no elevation in caspofungin concentrations occurred. Refer to Table 5. In addition, results from the 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 in adult patients with inducers of drug clearance, such as efavirenz, nevirapine, phenytoin, rifampicin, dexamethasone, or carbamazepine, use of a daily dose of 70 mg CANCIDAS should be considered.

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

ADVERSE EFFECTS

General

Hypersensitivity reactions have been reported (see PRECAUTIONS).

Clinical Adverse Experiences in Adult Patients

The overall safety of caspofungin was assessed in 1865 adult individuals who received single or multiple doses of caspofungin acetate: 564 febrile, neutropenic patients (empirical therapy study), 382 patients with invasive candidiasis, 297 patients with oesophageal 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 haematopoietic stem-cell transplantation. In the studies involving patients with documented *Candida* infections, the majority of the patients had serious underlying medical conditions (e.g. haematologic or other malignancy, recent major surgery,

HIV) requiring multiple concomitant medications. Patients in the non-comparative *Aspergillus* study often had serious predisposing medical conditions (e.g., bone marrow or peripheral stem cell transplants, haematologic malignancy, solid tumours or organ transplants) requiring multiple concomitant medications.

Empirical Therapy in Febrile, Neutropenic Patients

In the randomised, double-blinded empirical therapy study, patients received either CANCIDAS 50 mg/day (following a 70 mg loading dose) or AmBisome (3 mg/kg/day). Drug-related clinical adverse experiences occurring in ≥ 2% of the patients in either treatment group are presented in Table 6.

Table 6
Drug-Related* Clinical Adverse Experiences Among Patients with Persistent Fever and Neutropenia

Incidence ≥ 2% for at least one treatment group by Body System

	CANCIDAS** N=564 (percent)	AmBisome*** N=547 (percent)
Body as a Whole		
Abdominal Pain	1.4	2.4
Chills	13.8	24.7
Fever	17.0	19.4
Flushing	1.8	4.2
Perspiration/Diaphoresis	2.8	2.2
Cardiovascular System		
Hypertension	1.1	2.0
Tachycardia	1.4	2.4
Digestive System		
Diarrhoea	2.7	2.4
Nausea	3.5	11.3
Vomiting	3.5	8.6
Metabolism and Nutrition		
Hypokalaemia	3.7	4.2
Musculoskeletal System		
Back Pain	0.7	2.7
Nervous System & Psychiatric		
Headache	4.3	5.7
Respiratory System		
Dyspnoea	2.0	4.2
Tachypnoea	0.4	2.0
Skin & Skin Appendage		
Rash	6.2	5.3

* Determined by the investigator to be possibly, probably, or definitely drug-related.
** 70 mg on Day 1, then 50 mg daily for the remainder of treatment; daily dose was increased to 70 mg for 73 patients.
*** 3.0 mg/kg/day; daily dose was increased to 5.0 mg/kg for 74 patients.

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

To evaluate the effect of CANCIDAS and AmBisome on renal function, nephrotoxicity was defined as doubling of serum creatinine relative to baseline or an increase of ≥1 mg/dL in serum creatinine if baseline serum creatinine was above the upper limit of the normal range. Among patients whose baseline creatinine clearance was >30 mL/min, the incidence of nephrotoxicity was significantly lower in the group treated with CANCIDAS (2.6%) than in the group treated with AmBisome (11.5%)

Invasive Candidiasis

In an initial randomised, double-blinded invasive candidiasis study, patients received either CANCIDAS 50 mg/day (following a 70-mg loading dose) or amphotericin B, 0.6 to 1.0 mg/kg/day. Drug-related clinical adverse experiences occurring in ≥2% of the patients in either treatment group are presented in Table 7.

Table 7
Drug-Related Clinical Adverse Experiences Among Patients with Invasive Candidiasis*

Incidence ≥2% for at least one treatment group by Body System

	CANCIDAS 50 mg** N=114 (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		
Diarrhoea	2.6	0.8
Jaundice	0.9	3.2
Nausea	1.8	5.6
Vomiting	3.5	8.0
Metabolic/Nutritional/Immune		
Hypokalaemia	0.9	5.6
Nervous System & Psychiatric		
Tremor	1.8	2.4
Respiratory System		
Tachypnoea	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%).

In a second randomised, double-blinded invasive candidiasis study, patients received either CANCIDAS 50 mg/day (following a 70-mg loading dose) or CANCIDAS 150 mg/day. The primary endpoint for this study was the proportion of patients developing a significant drug-related adverse experience (defined as a serious drug-related adverse experience or a drug-related adverse experience leading to caspofungin discontinuation). The proportion of patients with a significant drug-related adverse experience was comparable in the 2 treatment groups: 1.9% (2/104) vs. 3.0% (3/100) in the CANCIDAS 50 mg/day and 150 mg/day groups, respectively (difference 1.1% [95% CI -4.1, 6.8]). The proportion of patients who experienced any drug-related adverse experience was also similar in the 2 treatment groups. Drug-related clinical

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

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

Adverse Experience (MedDRA v11.0 System Organ Class and Preferred Term)	CANCIDAS 50 mg† N=104 (percent)	CANCIDAS 150 mg N=100 (percent)
All Systems, Any Adverse Experience	**13.5**	**14.0**
General Disorders and Administration Site Conditions	**6.7**	**7.0**
Injection site erythema	0.0	2.0
Injection site phlebitis	3.8	2.0
Injection site swelling	1.0	2.0
Metabolism and Nutrition Disorders	**1.9**	**2.0**
Hypokalemia	1.0	2.0
Nervous System Disorders	**0.0**	**2.0**
Headache	0.0	2.0

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

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

Oesophageal and/or oropharyngeal candidiasis

Drug-related clinical adverse experiences occurring in ≥2% of patients with oesophageal and/or oropharyngeal candidiasis are presented in Table 9.

TABLE 9
Drug-related Clinical Adverse Experiences among Patients with Oesophageal and/or Oropharyngeal Candidiasis*

Incidence ≥2% for at least one treatment dose (per comparison) by Body System

	CANCIDAS 50 mg (N=83) percent	Fluconazole IV 200mg (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
Oedema/swelling	0.0	0.0	0.0	0.0	5.6
Oedema, 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
Peripheral Vascular System					
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
Cardiovascular System					
Tachycardia	0.0	0.0	1.3	0.0	4.5
Vasculitis	0.0	0.0	0.0	0.0	3.4
Digestive System					
Anorexia	0.0	0.0	1.3	0.0	3.4
Diarrhoea	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
Haemic & Lymphatic System					
Anaemia	0.0	0.0	3.8	0.0	9.0
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
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
Paraesthesia	0.0	0.0	1.3	3.1	1.1
Tremor	0.0	0.0	0.0	0.0	7.9
Respiratory System					
Tachypnoea	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.

Invasive aspergillosis

In the open-label, non-comparative 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 ≥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 oedema, adult respiratory distress syndrome (ARDS), and radiographic infiltrates.

Clinical Adverse Experiences in Paediatric Patients

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

TABLE 10
Drug-Related Clinical Adverse Experiences among Paediatric Patients*
Incidence ≥2% for at least one treatment dose by Body System

	CANCIDAS Any Dose** N=171 (percent)	CANCIDAS 50 mg/m^2*** N=56 (percent)	AmBisome 3 mg/kg*** N=26 (percent)
Cardiac Disorders			
Tachycardia	1.2	1.8	11.5
Gastrointestinal Disorders			
Nausea	0.0	0.0	3.8
Vomiting	0.6	1.8	7.7
General Disorders & Administration Site Conditions			
Adverse Drug Reaction	0.0	0.0	3.8
Catheter Site Pain	1.2	3.6	0.0
Chills	1.8	1.8	7.7
Fever	11.7	28.6	23.1
Hepatobiliary Disorders			
Hepatitis, toxic	0.0	0.0	3.8
Hyperbilirubinemia	0.0	0.0	3.8
Jaundice	0.0	0.0	3.8
Metabolism & Nutrition Disorders			
Hypokalemia	0.6	0.0	3.8
Nervous System Disorders			
Headache	2.9	8.9	0.0
Respiratory, Thoracic, & Mediastinal Disorders			
Dyspnea	0.0	0.0	3.8
Laryngospasm	0.0	0.0	3.8
Skin & Subcutaneous Tissue Disorders			
Angioneurotic edema	0.0	0.0	3.8
Circumoral edema	0.0	0.0	3.8
Pruritus	1.8	3.6	0.0
Rash	4.7	8.9	0.0
Vascular Disorders			
Flushing	1.8	3.6	0.0
Hypotension	1.8	3.6	3.8

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

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

***Laboratory values**:*

Adult Patients

Empirical Therapy in Febrile, Neutropenic Patients

Drug-related laboratory adverse experiences occurring in ≥ 2% of the patients in either treatment group are presented in Table 11.

TABLE 11
Drug-Related* Laboratory Adverse Experiences among Patients with Persistent Fever and Neutropenia

Incidence ≥ 2% for at least one treatment group by Laboratory Test Category

	CANCIDAS** N=564 (percent)	AmBisome*** N=547 (percent)
Blood Chemistry		
Alanine aminotransferase increased	8.7	8.9
Alkaline phosphatase increased	7.0	12.0
Aspartate aminotransferase increased	7.0	7.6
Direct serum bilirubin increased	2.6	5.2
Total serum bilirubin increased	3.0	5.2
Hypokalemia	7.3	11.8
Hypomagnesemia	2.3	2.6
Serum creatinine increased	1.2	5.5

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

** 70 mg on Day 1, then 50 mg daily for the remainder of treatment; daily dose was increased to 70 mg for 73 patients.

*** 3.0 mg/kg/day; daily dose was increased to 5.0 mg/kg for 74 patients.

The percentage of patients with either a drug-related clinical or a drug-related laboratory adverse experience was significantly lower among patients receiving CANCIDAS (54.4%) than among patients receiving AmBisome (69.3%). Furthermore, the incidence of discontinuation due to a drug-related clinical or laboratory adverse experience was significantly lower among patients treated with CANCIDAS (5.0%) than among patients treated with AmBisome (8.0%).

Invasive Candidiasis

Drug-related laboratory adverse experiences occurring in ≥2% of the patients in an initial invasive candidiasis study are presented in Table 12.

Table 12
Drug-Related Laboratory Adverse Experiences among Patients with Invasive Candidiasis*

Incidence ≥2% for at least one treatment group by Laboratory Test Category

	CANCIDAS 50 mg** N=114 (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
Haematology		
Haematocrit decreased	0.9	7.3
Haemoglobin 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; 3/114 (2.6%) in the CANCIDAS group and 29/125 (23.2%) in the amphotericin B group.

To evaluate the effect of CANCIDAS and amphotericin B on renal function, nephrotoxicity was defined as doubling of serum creatinine relative to baseline or an increase of ≥1 mg/dL in serum creatinine if baseline serum creatinine was above the upper limit of the normal range. In a subgroup of patients whose baseline creatinine clearance was >30 mL/min, the incidence of nephrotoxicity was significantly lower in the CANCIDAS group than in the amphotericin B group.

In a second randomised, double-blinded invasive candidiasis study, patients received either CANCIDAS 50 mg/day (following a 70-mg loading dose) or CANCIDAS 150 mg/day. Drug-related laboratory adverse experiences occurring in ≥2.0% of the patients in either treatment group are presented in Table 13.

TABLE 13
Drug-Related* Laboratory Adverse Experiences among Patients with Invasive Candidiasis
Incidence ≥2.0% for at Least One Treatment Group by System Organ Class or Preferred Term

Adverse Experience (MedDRA v11.0 System Organ Class and Preferred Term)	CANCIDAS 50 mg† N=104 (percent)	CANCIDAS 150 mg N=100 (percent)
All Systems, Any Adverse Experience	**7.8**	**7.1**
Alanine Aminotransferase Increased	2.0	2.0
Alkaline Phosphatase Increased	6.9	2.0
Aspartate Aminotransferase Increased	4.0	2.0

* Determined by the investigator to be possibly, probably, or definitely drug-related. Within any system organ class, individuals may experience more than 1 adverse experience
† Patients received CANCIDAS 70 mg on Day 1, then 50 mg daily for the remainder of their treatment

Oesophageal and/or oropharyngeal candidiasis

Drug-related laboratory abnormalities occurring in ≥2% of patients with oesophageal and/or oropharyngeal candidiasis are presented in Table 14.

TABLE 14
Drug-related Laboratory Abnormalities Reported among Patients with Oesophageal and/or Oropharyngeal Candidiasis (comparative studies)*
Incidence ≥2% (for at least one treatment dose) by Laboratory Test Category

	CANCIDAS 50 mg (N=163) (percent)	CANCIDAS 70 mg (N=65) (percent)	Fluconazole 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
Haematology				
Eosinophils increased	3.1	3.1	1.1	1.1
Haematocrit decreased	11.1	1.5	5.4	32.6
Haemoglobin 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.

Invasive aspergillosis

Drug-related laboratory abnormalities reported with an incidence ≥2% in patients treated with CANCIDAS in the non-comparative 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%).

The safety and efficacy of multiple doses up to 150 mg daily (range: 1 to 51 days; median: 14 days) have been studied in 100 adult patients with invasive candidiasis. CANCIDAS was generally well tolerated in these patients receiving CANCIDAS at this higher dose; however, the efficacy of CANCIDAS at this higher dose was generally similar to patients receiving the 50-mg daily dose of CANCIDAS.

Paediatric Patients

Table 15 shows the incidence of drug-related laboratory adverse experiences reported in ≥2.0% of paediatric patients in clinical studies. The overall laboratory safety profile in paediatric patients is comparable to that in adult patients. The most common drug-related laboratory adverse experiences in paediatric patients treated with CANCIDAS were increased ALT (6.5%) and increased AST (7.6%). None of the patients receiving CANCIDAS or AmBisome developed a serious drug-related adverse event or were discontinued from therapy due to a drug-related laboratory adverse experience.

TABLE 15
Drug-Related Laboratory Adverse Experiences among Paediatric Patients*
Incidence ≥2% for at least one treatment dose by Body System

	CANCIDAS Any Dose** N=171 (percent)	CANCIDAS 50 mg/m^2*** N=56 (percent)	AmBisome 3 mg/kg*** N=26 (percent)
Blood Chemistry Test			
Alanine aminotransferase (ALT) increased	6.5	3.6	0.0
Aspartate aminotransferase (AST) increased	7.6	1.8	0.0
Blood bilirubin increased	0.6	1.8	4.0
Blood phosphorus decreased	2.0	1.8	0.0
Blood potassium decreased	3.5	3.6	11.5
Blood sodium decreased	0.0	0.0	3.8
Direct bilirubin increased	0.0	0.0	6.3

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

Post-marketing experience

The following post-marketing adverse events have been reported:

Hepatobiliary: rare cases of hepatic dysfunction
Skin and subcutaneous tissue disorders: toxic epidermal necrolysis and Steven-Johnson syndrome
Cardiovascular: swelling and peripheral oedema
Metabolic: hypercalcaemia; gamma-glutamyltransferase increased.

DOSAGE AND ADMINISTRATION

Dosage Recommendations

CANCIDAS should be administered in adult patients by slow intravenous infusion over approximately 1 hour (refer to Reconstitution section for dilution recommendations).

Table 16
Dosing Recommendations in Adult Patients

	Loading Dose	**Maintenance dose**
Empirical Therapy		
Normal hepatic function or mild hepatic insufficiency*	70 mg on day 1	50 mg daily
Moderate hepatic insufficiency **	70 mg on day 1	35 mg daily
Invasive candidiasis		
Normal hepatic function or mild hepatic insufficiency*	70 mg on day 1	50 mg daily
Moderate hepatic insufficiency **	70 mg on day 1	35 mg daily
Oesophageal		
Normal hepatic function or mild hepatic insufficiency*	Not required	50 mg daily
Moderate hepatic insufficiency**	Not required	35 mg daily
Invasive aspergillosis		
Normal hepatic function or mild hepatic insufficiency*	70 mg on day 1	50 mg daily
Moderate hepatic insufficiency **	70 mg on day 1	35 mg daily

*Mild hepatic insufficiency: Child-Pugh score 5 to 6
**Moderate hepatic insufficiency: Child Pugh score 7 to 9

General Recommendations in Adult Patients

Empirical Therapy
Duration of treatment should be based on the patient's clinical response. Empirical therapy should be continued until resolution of neutropenia, which is generally expected to occur within 28 days. 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.

Candidiasis
- Invasive: 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.
- Oesophageal: Increasing doses of CANCIDAS above 50 mg daily provided no additional benefit in the treatment of oesophageal candidiasis.

Invasive Aspergillosis
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.

Concomitant Therapy with Inducers of Drug Clearance
When CANCIDAS is co-administered in adult patients with inducers of drug clearance, such as efavirenz, nevirapine, phenytoin, rifampicin, dexamethasone or carbamazepine, use of a daily dose of 70 mg of CANCIDAS should be considered.

Hepatic Insufficiency
- Adult patients with mild hepatic insufficiency (Child-Pugh score 5 to 6) do not need a dosage adjustment.
- Adult patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), require an adjustment to maintenance dosage-refer to Table16.
- There is no clinical experience in adult patients with severe hepatic insufficiency (Child-Pugh score >9) (see PHARMACOLOGY, Pharmacokinetics, Special Populations) and in paediatric patients with any degree of hepatic insufficiency.

Renal Insufficiency
No dosage adjustment is necessary for patients with renal insufficiency. Caspofungin is not dialysable, thus supplementary dosing is not required following haemodialysis (see PHARMACOLOGY, Pharmacokinetics, Special Populations).

Paediatric Patients
CANCIDAS should be administered in paediatric patients (3 months to 17 years of age) by slow IV infusion over approximately 1 hour. Dosing in paediatric patients (3 months to 17 years of age) should be based on the patient's body surface area (see Instructions for Use in Paediatric Patients, Mosteller[2] Formula).

For all indications, a single 70-mg/m^2 loading dose (not to exceed an actual dose of 70 mg) should be administered on Day 1, followed by 50 mg/m^2 daily thereafter (not to exceed an actual dose of 70 mg daily). Duration of treatment should be individualised to the indication, as described for each indication in adults (see **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.

The efficacy and safety of CANCIDAS have not been sufficiently studied in clinical trials involving neonates and infants below 12 months of age. Caution is advised

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

when treating this age group. Limited data suggest that CANCIDAS at 25 mg/m^2 daily in neonates and infants (less than 3 months of age) and 50 mg/m^2 daily in young children (3 to 11 months of age) can be considered.

When CANCIDAS is co-administered to paediatric patients with inducers of drug clearance, such as rifampicin, 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) may need to be considered depending on the clinical response.

Reconstitution of CANCIDAS

The reconstituted vial of CANCIDAS must be further diluted prior to administration. DO NOT USE DILUENTS CONTAINING GLUCOSE as CANCIDAS is not stable in diluents containing glucose.

CANCIDAS should be administered by slow IV infusion of approximately 1 hour. It contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue.

Do not mix or co-infuse CANCIDAS with other medications as there is no data available on the compatibility of CANCIDAS with other intravenous substances, additives, or medications.

INSTRUCTIONS FOR USE IN ADULTS

Step 1: Reconstitution of vials
To reconstitute the powdered drug, bring the refrigerated vial of CANCIDAS to room temperature and aseptically add 10.5 mL of 0.9% Sodium Chloride Injection or Water for Injections. 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 discolouration. This reconstituted solution is chemically and physically stable for up to 1 hour when held below 25°C. However, to reduce microbiological hazard, use as soon as practicable after dilution and if storage is necessary, hold at 2-8°C for not more than 1 hour.

Step 2: Addition of reconstituted CANCIDAS to infusion solution
The patient infusion solution is prepared by aseptically adding the appropriate amount of reconstituted drug (as shown in Table17) to a 250 mL intravenous PVC bag or glass bottle of 0.9% Sodium Chloride Injection. Reduced volume infusions in 100 mL may be used, when medically necessary, for 50 mg or 35 mg daily doses.

Visually inspect the infusion solution for particulate matter or discolouration. Do not use if the solution is cloudy or precipitated. This infusion solution is chemically and physically stable for 24 hours when stored below 25°C. However, to reduce microbiological hazard, use as soon as practicable after dilution and if storage is necessary, hold at 2-8°C for not more than 24 hours. CANCIDAS should be administered by slow intravenous infusion over approximately 1 hour. It contains no antimicrobial agent. Use once only and discard any residue.

Table 17:
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 infusion sodium chloride 0.9%) final concentration	Reduced Volume Infusion (reconstituted CANCIDAS added to 100mL infusion sodium chloride 0.9% final concentration
70 mg (from one 70 mg vial)	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 (from one 50 mg vial)	10 mL	0.20 mg/mL	0.47 mg/mL
35 mg (from one 50 mg vial)	7 mL	0.14 mg/mL	0.34 mg/mL
35 mg (from one 70 mg vial)	5 mL	0.14 mg/mL	0.34 mg/mL

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

INSTRUCTIONS FOR USE IN PAEDIATRIC PATIENTS

Calculation of Body Surface Area (BSA) for paediatric 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/m^2 infusion for paediatric patients 3 months of age or older (using a 70-mg vial)

1. Determine the actual loading dose to be used in the paediatric 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 or Sterile Water for Injection[a] This reconstituted solution may be stored for up to one hour at ≤25°C.[b] This will give a final caspofungin concentration in the vial of 7.2 mg/mL.
4. Remove the volume of drug equal to the calculated loading dose (Step 1) from the vial. Aseptically transfer this volume (mL)[c] of reconstituted CANCIDAS to an IV bag (or bottle) containing 250 mL of 0.9%, 0.45%, or 0.225% Sodium Chloride Injection, or Lactated 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 ≤25°C or within 24 hours if stored refrigerated at 2 to 8°C.

5. If the calculated loading dose is <50 mg, then the dose may be prepared from the 50-mg vial [follow Steps 2-4 from *Preparation of the 50 mg/m^2 infusion for paediatric patients 3 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/m^2 infusion for paediatric patients 3 months of age* or older *(using a 50-mg vial)

1. Determine the daily maintenance dose to be used in the paediatric 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 (mg)

   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 or Sterile Water for Injection[a] This reconstituted solution may be stored for up to one hour at ≤25°C.[b] This will give a final caspofungin concentration in the vial of 5.2 mg/mL.
4. Remove the volume of drug equal to the calculated loading dose (Step 1) from the vial. Aseptically transfer this volume (mL)[c] of reconstituted CANCIDAS to an IV bag (or bottle) containing 250 mL of 0.9%, 0.45%, or 0.225% Sodium Chloride Injection, or Lactated 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 ≤25°C or within 24 hours if stored refrigerated at 2 to 8°C.
5. If the actual daily maintenance dose is > 50 mg, then the dose may be prepared from the 70-mg vial [follow steps 2-4 from Preparation of the 70 mg/m^2 infusion for paediatric patients 3 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/L.

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 discolouration 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 labelled vial dose (70 mg or 50 mg) when 10 mL is withdrawn from the vial.

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, 150 mg daily up to 51 days has been administered to 100 healthy patients and was generally well-tolerated. Caspofungin is not dialysable.

PRESENTATION AND STORAGE CONDITIONS

CANCIDAS is available as a white to off white lyophilised compact powder for infusion in single use vials of 50 mg and 70 mg.

The lyophilised vials of CANCIDAS should be stored at 2-8°C, refrigerate, do not freeze.

Reconstituted vials of CANCIDAS may be stored for one hour prior to preparation of the infusion solution, and the final patient infusion solution in the IV bag or bottle can be stored for up to 24 hours. To reduce microbiological hazard, it is recommended to use as soon as practicable after reconstitution/dilution and if storage is necessary, to hold at 2-8°C.

SPONSOR

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POISONS SCHEDULE

Schedule 4 – Prescription Medicine

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