SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

CANCIDAS® 50 mg Lyophilised Powder for Solution for Infusion

CANCIDAS® 70 mg Lyophilised Powder for Solution for Infusion

COMPOSITION

Each vial of CANCIDAS 50 mg contains 50 mg of caspofungin anhydrous free base, equivalent to 55,5 mg of caspofungin acetate.

Each vial of CANCIDAS 70 mg contains 70 mg of caspofungin anhydrous free base, equivalent to 77,7 mg of caspofungin acetate.

Excipients: Sucrose, mannitol, glacial acetic acid, sodium hydroxide and water for injection.

Contains sugar (sucrose and mannitol).

PHARMACOLOGICAL CLASSIFICATION

A.20.2.2. Antimicrobial (chemotherapeutic agents): Fungicides

PHARMACOLOGICAL ACTION

Mechanism of action

Caspofungin acetate, the active ingredient of CANCIDAS, inhibits the synthesis of beta (1,3)-D-glucan, an essential component of the cell wall of many filamentous fungi and yeast. Beta (1,3)-D-glucan is not present in mammalian cells.

Pharmacokinetics

Distribution

Plasma concentrations of caspofungin decline in a polyphasic manner following single 1 hour intravenous infusions. A short alpha-phase occurs immediately post-infusion, followed by a beta-phase with a 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 10-fold. An additional gamma-phase also occurs (half-life 40 to 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.

Metabolism

Caspofungin is slowly metabolised by hydrolysis and N-acetylation. Caspofungin also undergoes spontaneous chemical degradation to an open-ring peptide compound. At later time points (≥ 5 days post-dose), there is a low level (≤ 7 picomoles/mg protein or ≤ 1,3 % of administered dose) of covalent binding of radio-label 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.

Elimination

Two single-dose radio-labelled 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 6 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 medicine 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 (approximately 1,4 % of dose). Renal clearance of parent substance is low (approximately 0,15 ml/min).

Paediatric Patients

CANCIDAS has been studied in five prospective studies involving patients under 18 years of age, including three paediatric pharmacokinetic studies (initial study in adolescents [12 to 17 years of age] and children [2 to 11 years of age] followed by a study in younger patients [3 to 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 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 have not been adequately studied in prospective clinical trials involving neonates and infants under 3 months of age.

Clinical Studies

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

Invasive Candidiasis

Two hundred thirty-nine patients were enrolled in an initial study to compare CANCIDAS and amphotericin B for the treatment of invasive candidiasis. The most frequent diagnoses were bloodstream infections (candidaemia) (83 %) and *Candida* peritonitis (10 %). CANCIDAS 50 mg once

daily was administered following a 70 mg loading dose, while amphotericin B was administered at 0,6 to 0,7 mg/kg/day to non-neutropenic patients or 0,7 to 1,0 mg/kg/day to neutropenic patients. A favourable response required both symptom resolution and microbiological clearance of the *Candida* infection. Two hundred twenty-four patients were included in the primary efficacy analysis of response at the end of IV study therapy; favourable response rates for the treatment of invasive candidiasis were comparable for CANCIDAS (73 % [80/109]) and amphotericin B (62 % [71/115]). One hundred eighty-five patients who received at least 5 days of IV study therapy were included in a predefined efficacy analysis to support the primary analysis; in this analysis, CANCIDAS (favourable response rate 81 % [71/88]) was statistically superior to amphotericin B (65 % [63/97]) at the end of IV study therapy. Among patients with candidaemia, the favourable response rates at the end of IV study therapy were 72 % (66/92) in the CANCIDAS group and 63 % (59/94) in the amphotericin B group in the primary efficacy analysis, and were 80 % (57/71) in the CANCIDAS group and 65 % (51/79) in the amphotericin B group in the predefined efficacy analysis to support the primary analysis. In both analyses, CANCIDAS was comparable to amphotericin B in the treatment of 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 favourable 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]).

Invasive Aspergillosis

Sixty-nine patients (age range: 18 to 80) with pulmonary or extrapulmonary invasive aspergillosis (IA) were enrolled in an open-label, non-comparative study to evaluate the safety, tolerability and efficacy

of CANCIDAS. Enrolled patients were either refractory to (disease progression or failure to improve with other therapies) or intolerant of (nephrotoxicity, infusion-related reactions or other acute reactions) amphotericin B, lipid formulations of amphotericin B and itraconazole. Pulmonary disease patients had definite or probable IA. Patients with extrapulmonary disease had definite IA. Patients were administered a single 70 mg loading dose followed by 50 mg daily. The mean duration of therapy was 33,7 days (range: 1 to 162 days). Eighty-four percent of patients were refractory to previous antifungal therapy and most had haematologic malignancies or allogeneic bone marrow transplant.

An independent expert panel evaluated patient data and determined that 41 % (26/63) of patients receiving at least one dose of CANCIDAS had a favourable response, defined as either complete resolution (complete response) or clinically meaningful improvement (partial response) of all signs and symptoms and attributable radiographic findings. Stable, non-progressive disease was considered to be an unfavourable response. For those patients who received more than 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.

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 liposomal amphoterin B (3 mg/kg IV daily) in a 2:1 treatment fashion (56 on caspofungin, 26 on liposomal amphoterin B) 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. 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 results, adjusted for strata, were as follows: 46,6 % (26/56) for CANCIDAS and 32,2 % (8/25) for liposomal amphoterin B. 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 liposomal amphoterin B 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 "**PHARMACOLOGICAL ACTION, Clinical Studies, Invasive 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.

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.

Table 1: Susceptibility Interpretive Criteria for Caspofungin against *Candida* species

Pathogen	Broth Microdilution MIC* (μg/ml) at 24 hours		
	Susceptible	**Indeterminate**	**Resistant**
Candida species	≤ 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.

† The current absence of data on caspofungin-resistant isolates precludes defining any categories other than “Susceptible”. Isolates yielding test results suggestive of a “Non-Susceptible” category should be retested, and if the result is confirmed, the isolate should be submitted to a reference laboratory for further testing.

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

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. In a lethal, rat pulmonary-infection model with *A. fumigatus*, caspofungin was highly active in the prevention and treatment of pulmonary aspergillosis.

Cross-resistance

Caspofungin acetate is active against strains of *Candida* with intrinsic or acquired resistance to fluconazole, amphotericin B or flucytosine consistent with their different mechanisms of action.

Resistance

Mutants of *Candida* with reduced susceptibility to caspofungin have been identified in some patients during treatment.

A caspofungin MIC of ≤ 2 μg/ml ("Susceptible" per **Table 1**) using the CSLI M27-A3 method indicates that the *Candida* isolate is likely to be inhibited if caspofungin therapeutic concentrations are achieved; there is insufficient treatment outcome information on isolates with reduced caspofungin susceptibility to define categories other than susceptible. Breakthrough infections with *Candida* isolates requiring caspofungin concentrations > 2 μg/ml for growth inhibition have developed in a mouse model of *C. albicans* infection and in some patients with *Candida* infections. Some of these isolates had mutations in the FKS1 gene.

Development of *in vitro* resistance to caspofungin by *Aspergillus* species has not been identified. In clinical experience, resistance in patients with invasive aspergillosis has not been observed. The incidence of resistance in various clinical isolates of *Candida* and *Aspergillu*s species is unknown.

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.

Elderly

The plasma concentration of caspofungin in healthy older men and women (65 years of age or more) was increased (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. However, no dosage adjustment is necessary for elderly patients (65 years of age or more).

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 area under the curve (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. In a multiple-dose study, a dose reduction of the daily dose to 35 mg in moderate hepatic impairment has been shown to provide an AUC similar to that obtained in subjects with normal hepatic function receiving the standard regime. CANCIDAS has not been studied in severe hepatic insufficiency.

INDICATIONS

CANCIDAS is indicated in adults for:

- Empirical therapy for presumed fungal infections in febrile, neutropenic patients.
- Treatment of invasive candidiasis, including candidaemia.
- Treatment of oesophageal candidiasis where IV antifungal therapy is appropriate.
- Treatment of oropharyngeal candidiasis where IV antifungal therapy is appropriate.
- Treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies, including amphotericin B, lipid formulations of amphotericin B and itraconazole.

Paediatric use

The safety and effectiveness of CANCIDAS in paediatric patients 3 months to 17 years of age are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in paediatric patients, and additional data from prospective studies in paediatric patients 3 months to 17 years of age.

The efficacy and safety of CANCIDAS have not been adequately studied in prospective clinical trials involving neonate and infants under 3 months of age.

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

CONTRAINDICATIONS

- CANCIDAS is contraindicated in patients with hypersensitivity to any component of this product.
- CANCIDAS has not been studied in severe hepatic insufficiency.

WARNINGS AND SPECIAL PRECAUTIONS

Concomitant use of CANCIDAS with ciclosporin has been evaluated in adult healthy volunteers and in adult patients. Some healthy adult subjects who received two 3 mg/kg doses of ciclosporin with caspofungin showed transient increases in ALT and AST of ≤ 3-fold the upper limit of normal (ULN) that resolved with discontinuation of these medicines. There was also an increase of approximately 35 % in the area under the curve (AUC) of caspofungin when CANCIDAS and ciclosporin were co-administered; blood levels of ciclosporin remained unchanged.

Anaphylaxis has been reported during administration of CANCIDAS. If this occurs CANCIDAS should be discontinued and appropriate treatment administered. Possible histamine-mediated symptoms including reports of 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 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.

Effects on Ability to Drive and Use Machines

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

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 medicines. Caspofungin is not a substrate for P-glycoprotein and is a poor substrate for cytochrome P450 enzymes.

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

In two adult clinical studies, ciclosporin (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 liver. CANCIDAS did not increase the plasma levels of ciclosporin. There were transient increases in liver ALT and AST when CANCIDAS and ciclosporin were co-administered. In a retrospective study of 40 patients treated during marketed use with CANCIDAS and/or ciclosporin for 1 to 290 days (median 17,5 days), no serious hepatic adverse events were noted (see **"WARNINGS AND SPECIAL 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 interaction studies in healthy adult volunteers indicate that rifampicin both induces and inhibits caspofungin disposition with net induction at steady state. In addition, results from population pharmacokinetic screening in adults suggests that co-administration of other inducers of medicine 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 medicine 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 medicine clearance, such as efavirenz, nevirapine, rifampicin, dexamethasone, phenytoin or carbamazepine, use of a daily dose of 70 mg of CANCIDAS should be considered (see **"DOSAGE AND DIRECTIONS FOR USE"**).

In paediatric 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 paediatric patients will have similar reductions with inducers as seen in adults. When CANCIDAS is co-administered to paediatric patients with inducers of medicine 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.

PREGNANCY AND LACTATION

Pregnancy

CANCIDAS should not be used during pregnancy as there is no clinical experience involving pregnant women.

Breastfeeding

It is not known whether CANCIDAS is excreted in human milk; therefore, women receiving CANCIDAS should not breastfeed.

DOSAGE AND DIRECTIONS FOR USE

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 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 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.

Invasive Candidiasis

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

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.

Oesophageal and Oropharyngeal 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 suggests 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 of CANCIDAS, should be considered (see **"INTERACTIONS"**).

Patients with Hepatic Insufficiency

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

experience in adult patients with severe hepatic insufficiency (Child-Pugh score > 9) and in paediatric patients with any degree of hepatic insufficiency.

Paediatric Patients

CANCIDAS should be administered in children and adolescents (3 months to 17 years of age) by slow IV infusion over approximately 1 hour. Dosing in children and adolescents (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 [1]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).

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

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 paediatric 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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Reconstitution of CANCIDAS

DO NOT USE ANY DILUENTS CONTAINING DEXTROSE (alpha-D-GLUCOSE), as CANCIDAS is not stable in diluents containing dextrose. DO NOT MIX OR CO-INFUSE CANCIDAS WITH ANY

OTHER MEDICATIONS, as there is no data available on the compatibility of CANCIDAS with other intravenous substances, additives or medications. Visually inspect the infusion solution for particulate matter or discolouration.

INSTRUCTIONS FOR USE IN ADULTS

Step 1. Reconstitution of vials

To reconstitute the powdered medicine, bring the refrigerated 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 discolouration. This reconstituted solution may be stored for up to 24 hours at or below 25 °C.

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 has precipitated. This infusion solution must be used within 24 hours if stored at or below 25 °C or within 48 hours if stored refrigerated at 2 to 8 °C. 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

Standard 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 hepatic insufficiency

(from one 70 mg vial)

5 ml

0,14 mg/ml

0,34 mg/ml

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 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):

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

Preparation of the 70 mg/m^2 infusion for paediatric patients > 3 months of age (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, Sterile Water for Injection or 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 25 °C. [b]This will give a final caspofungin concentration in the vial of 7,2 mg/ml.

4. Remove the volume of medicine equal to the calculated loading dose (Step 1) from the vial. Aseptically transfer this volume (ml)[c] of reconstituted CANCIDAS to an IV bag (or bottle) containing 250 ml of 0,9 %, 0,45 %, or 0,225 % Sodium Chloride Injection or Lactated Ringer's Injection. Alternatively, the volume (ml)[c] of reconstituted CANCIDAS can be added to a reduced volume of 0,9 %, 0,45 %, or 0,225 % Sodium Chloride Injection or Lactated Ringer's Injection, not to exceed a final concentration of 0,5 mg/ml. This infusion solution must be used within 24 hours if stored at or below 25 °C or within 48 hours if stored refrigerated at 2 to 8 °C.

5. If the calculated loading dose is less than 50 mg, then the dose may be prepared from the 50 mg vial [follow Steps 2 to 4 from **"Preparation of the 50 mg/m^2 infusion for paediatric patients > 3 months of age (using a 50 mg vial)]"**. The final caspofungin concentration in the 50 mg vial after reconstitution is 5,2 mg/ml.

Preparation of the 50 mg/m^2 infusion for paediatric patients > 3 months of age (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

The daily maintenance dose should not exceed 70 mg regardless of the patient's calculated dose.

2. Equilibrate the refrigerated vial of CANCIDAS to room temperature.

3. Aseptically add 10,5 ml of 0,9 % Sodium Chloride Injection, Sterile Water for Injection or Bacteriostatic Water for Injection with methylparaben and propylparaben 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. [b]This will give a final caspofungin concentration in the vial of 5,2 mg/ml.

4. Remove the volume of medicine equal to the calculated loading dose (Step 1) from the vial. Aseptically transfer this volume (ml)[c] of reconstituted CANCIDAS to an IV bag (or bottle)

containing 250 ml of 0,9 %, 0,45 %, or 0,225 % Sodium Chloride Injection or Lactated Ringer's Injection. Alternatively, the volume (ml)[c] of reconstituted CANCIDAS can be added to a reduced volume of 0,9 %, 0,45 %, or 0,225 % Sodium Chloride Injection or Lactated Ringer's Injection, not to exceed a final concentration of 0,5 mg/ml. This infusion solution must be used within 24 hours if stored at or below 25 °C or within 48 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 to 4 from **"Preparation of the 70 mg/m^2 infusion for paediatric patients > 3 months of age (using a 70 mg vial)]"**. The final caspofungin concentration in the 70 mg vial after reconstitution is 7,2 mg/ml.

Preparation notes

[a]The white to off-white 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 solution if 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.

SIDE EFFECTS

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

Adult patients

The following adverse events were reported:

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

Blood and lymphatic system disorders

Common: Anaemia

Nervous system disorders

Common: Headache

Vascular disorders

Common: Phlebitis/thrombophlebitis

Respiratory, thoracic and mediastinal disorders

Common: Dyspnoea

Gastrointestinal disorders

Common: Nausea, diarrhoea, vomiting

Skin and subcutaneous tissue disorders

Common: Rash, pruritus, sweating, erythema

Musculoskeletal and connective tissue disorders

Common: Arthralgia

General disorders and administration site conditions

Very common: Fever

Common: Chills, infusion-site pruritus

Investigations

Common: Elevated liver test values (aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, direct and total bilirubin) decreased haemoglobin, decreased haematocrit, low potassium, low albumin, decreased white blood cells.

Paediatric Patients

In clinical studies, 171 paediatric patients 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.

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

Common (≥ 1/100, < 1/10)

Nervous system disorders

Common: Headache

Cardiac disorders

Common: Tachycardia

Vascular disorders

Common: Flushing, hypotension

Skin and subcutaneous tissue disorders

Common: Rash, pruritus

General disorders and administration site conditions

Common: Fever, chills, catheter site pain

Investigations

Common: Elevated liver enzyme levels (AST, ALT)

Post-Marketing experience

The following post-marketing adverse events have been reported:

Hepatobiliary disorders: Hepatic dysfunction

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis and Stevens-Johnson syndrome

Cardiovascular: Swelling and peripheral oedema

Investigations: Hypercalcaemia, gamma-glutamyltransferase increased.

Adult Patients

Other medicine-related laboratory abnormalities reported in adult patients were low albumin, low potassium and decreased white blood cells.

Paediatric Patients

Other drug-related laboratory abnormalities reported in paediatric patients were decreased potassium, hypomagnesaemia, increased glucose, decreased phosphorus, increased phosphorus and increased eosinophils.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

In clinical studies, the highest dose was 210 mg, which was administered as a single dose to 6 adult healthy subjects, and was generally well tolerated. In addition, a dose of 150 mg once daily up to 51 days has been administered to 100 adult patients and was generally well tolerated. Caspofungin is not dialysable.

IDENTIFICATION

Unopened vials

Each vial of CANCIDAS contains a solid white to off-white cake.

Reconstituted CANCIDAS in vials

Clear solution essentially free from visible particles.

Diluted product for infusion

Clear solution essentially free from visible particles.

PRESENTATION

CANCIDAS 50 mg and 70 mg lyophilised powder for solution for infusion are supplied in 10 ml clear glass vials.

STORAGE INSTRUCTIONS

Storage of unopened vials

The lyophilised compact powder in vials should be stored at 2 to 8 °C.

Storage of reconstituted CANCIDAS in vials

Reconstituted CANCIDAS may be stored at or below 25 °C 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 for up to 24 hours, or for up to 48 hours when refrigerated at 2 to 8 °C.

Do not freeze.

Keep out of reach of children.

REGISTRATION NUMBERS

CANCIDAS 50 mg: 37/20.2.2/0544

CANCIDAS 70 mg: 37/20.2.2/0545

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

MSD (Pty) Ltd

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