CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-227

APPROVED DRAFT LABELING

INTRAVENOUS INFUSION (not for IV Bolus Injection)

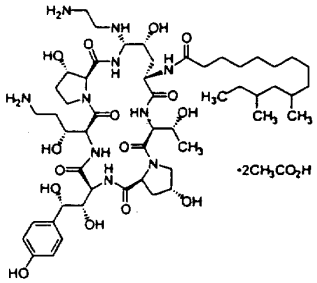
CANCIDAS®

(caspofungin acetate) FOR INJECTION

DESCRIPTION

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

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



CLINICAL PHARMACOLOGY

Pharmacokinetics

Distribution

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

Metabolism

Caspofungin is slowly metabolized by hydrolysis and N-acetylation. Caspofungin also undergoes spontaneous chemical degradation to an open-ring peptide compound, L-747969. At later time points (5 to 20 days postdose), there is a low level (3 to 7 picomoles/mg protein, or 0.6 to 1.3% of administered dose)

of covalent binding of radiolabel in plasma following single-dose administration of [^{3}H] caspofungin acetate, which may be due to two reactive intermediates formed during the chemical degradation of caspofungin to L-747969. Additional metabolism involves hydrolysis into constitutive amino acids and their degradates, including dihydroxyhomotyrosine and N-acetyl-dihydroxyhomotyrosine. These two tyrosine derivatives are found only in urine, suggesting rapid clearance of these derivatives by the kidneys.

Excretion

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

Special Populations

Gender

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

Geriatric

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

Race

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

Renal Insufficiency

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

Hepatic Insufficiency

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

Pediatric Patients

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

MICROBIOLOGY

Mechanism of Action

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

Activity in vitro

Caspofungin exhibits *in vitro* activity against *Aspergillus fumigatus, Aspergillus flavus,* and *Aspergillus terreus*. Susceptibility testing was performed according to the National Committee for Clinical Laboratory Standards (NCCLS) proposed method (M38-P). Standardized susceptibility testing methods for β (1,3)-D-glucan synthesis inhibitors have not been established, and results of susceptibility studies do not correlate with clinical outcome.

Activity in vivo

Caspofungin, administered parenterally to immunocompetent and immunosuppressed rodents, as long as 24 hours after disseminated or pulmonary infection with *Aspergillus fumigatus*, has shown prolonged survival, which has not been consistently associated with a reduction in mycological burden.

Drug Resistance

In vitro resistance development to caspofungin by *Aspergillus* species has not been studied. In limited clinical experience, drug resistance in patients with invasive aspergillosis has not been observed. The incidence of drug resistance by various clinical isolates of *Aspergillus* species is unknown.

Drug Interactions

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

CLINICAL STUDIES

Invasive Aspergillosis

Sixty-nine patients between the ages of 18 and 80 with invasive aspergillosis were enrolled in an open-label, noncomparative study to evaluate the safety, tolerability, and efficacy of CANCIDAS. Enrolled patients had previously been refractory to or intolerant of other antifungal therapy(ies). Refractory patients were classified as those who had disease progression or failed to improve despite therapy for at least 7 days with amphotericin B, lipid formulations of amphotericin B, itraconazole, or an investigational azole with reported activity against *Aspergillus*. Intolerance to previous therapy was defined as a doubling of creatinine (or creatinine ≥2.5 mg/dL while on therapy), other acute reactions, or infusion-related toxicity. To be included in the study, patients with pulmonary disease must have had definite (positive tissue histopathology or positive culture from tissue obtained by an invasive procedure) or probable (positive radiographic or computed tomography evidence with supporting culture from bronchoalveolar lavage or sputum, galactomannan enzyme-linked immunosorbent assay, and/or polymerase chain reaction) invasive aspergillosis. Patients with extrapulmonary disease had to have definite invasive aspergillosis. The definitions were modeled after the Mycoses Study Group Criteria.[1] Patients were administered a single 70-mg loading dose of CANCIDAS and subsequently dosed with 50 mg daily. The mean duration of therapy was 33.7 days, with a range of 1 to 162 days.

An independent expert panel evaluated patient data, including diagnosis of invasive aspergillosis, response and tolerability to previous antifungal therapy, treatment course on CANCIDAS, and clinical outcome.

A favorable response was defined as either complete resolution (complete response) or clinically meaningful improvement (partial response) of all signs and symptoms and attributable radiographic findings. Stable, nonprogressive disease was considered to be an unfavorable response.

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

[1] Denning DW, Lee JY, Hostetler JS, et al. NIAID Mycoses Study Group multicenter trial of oral itraconazole therapy for invasive aspergillosis. *Am J Med* 1994;97:135-144.

antifungal therapy and 10 (16%) were intolerant. Forty-five patients had pulmonary disease and 18 had extrapulmonary disease. Underlying conditions were hematologic malignancy (N=24), allogeneic bone marrow transplant or stem cell transplant (N=18), organ transplant (N=8), solid tumor (N=3), or other conditions (N=10). All patients in the study received concomitant therapies for their other underlying conditions. Eighteen patients received tacrolimus and CANCIDAS concomitantly, of whom 8 also received mycophenolate mofetil.

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

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

INDICATIONS AND USAGE

CANCIDAS is indicated for the treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies (i.e., amphotericin B, lipid formulations of amphotericin B, and/or itraconazole).

CANCIDAS has not been studied as initial therapy for invasive aspergillosis.

CONTRAINDICATIONS

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

WARNINGS

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

PRECAUTIONS

General

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

The safety information on treatment durations longer than 2 weeks is limited, however, available data suggest that CANCIDAS continues to be well tolerated with longer courses of therapy (68 patients received from 15 to 60 days of therapy; 12 patients received from 61 to 162 days of therapy).

Drug Interactions

Studies *in vitro* show that caspofungin acetate is not an inhibitor of any enzyme in the cytochrome P450 (CYP) system. In clinical studies, caspofungin did not induce the CYP3A4 metabolism of other

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