Drugs 2001; 61 (8): 1121-1129
0012-6667/01/0008-1121/$27.50/0



# Caspofungin

*Gillian M. Keating* and *Blair Jarvis*

Adis International Limited, Auckland, New Zealand

## Contents



## Abstract

▲ Caspofungin is the first in a new class of antifungal agents, the glucan synthesis inhibitors, that interfere with fungal cell wall synthesis.

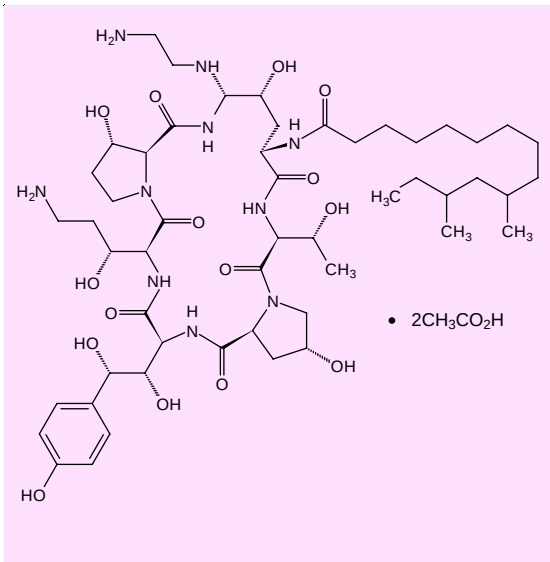
▲ Caspofungin exhibited *in vitro* and *in vivo* efficacy against a wide range of fungi and yeasts including *Aspergillus* and *Candida* species.

▲ A complete or partial response to caspofungin therapy was seen in 40.7% of immunocompromised adults with invasive aspergillosis who did not respond to, or did not tolerate, other antifungal agents in a noncomparative multicentre study.

▲ Caspofungin was effective in patients with oropharyngeal or oesophageal candidiasis, according to the preliminary results of 2 randomised double-blind trials.

▲ Caspofungin was generally well tolerated in a multicentre noncomparative trial involving patients with invasive aspergillosis. One or more drug-related clinical adverse effects were experienced by 13.8% of caspofungin recipients (the most common were fever, nausea, vomiting and complications associated with the vein into which caspofungin was infused). The tolerability of caspofungin appeared to be better than that of amphotericin B and similar to that of fluconazole in double-blind, randomised trials involving patients with mucosal candidiasis.

| Features and properties of caspofungin (MK-0991; L-743,872) | |
|---|---|
| **Approved Indications** | |
| Treatment of invasive aspergillosis in patients who are refractory to, or do not tolerate, conventional antifungal agents | |
| **Mechanism of action** | |
| Interferes with fungal cell wall synthesis by inhibiting the synthesis of β-(1,3)-D-glucan | |
| **Dosage and administration** | |
| Recommended dosage | 70mg loading dose followed by 50 mg/day maintenance dose |
| Route of administration | Intravenous infusion |
| Frequency of administration | Once daily |
| **Pharmacokinetic profile (after a single 70mg dose)** | |
| Plasma concentration at 1 hour | 10.45 mg/L |
| Plasma concentration at 24 hours | 1.19 mg/L |
| Area under the plasma concentration-time curve | 104.79 mg/L • h |
| Plasma protein binding | ≈96% |
| Systemic plasma clearance | 0.72 L/h |
| Excretion | Hepatic metabolism is the primary route of excretion |
| Elimination half-life | 9-11h |
| **Adverse events** | |
| The most common adverse effects associated with caspofungin therapy were fever, nausea, vomiting and complications related to the vein into which the drug was infused. | |




**Caspofungin**

The incidence of invasive fungal infections has been steadily increasing over the past 2 decades.[1] In part, this is because of the increasing numbers of patients whose immune systems are compromised secondary to factors such as intensive antineoplastic therapy, immunosuppressive therapy and AIDS. *Aspergillus* and *Candida* species are the most common causes of invasive fungal infection in immunocompromised patients.[2] Caspofungin is the first in a new class of antifungal agents, the glucan synthesis inhibitors, and has been developed for use in fungal infections such as invasive aspergillosis and *Candida* infections.

## 1. Pharmacodynamic Profile

### Mechanism of Action

• The glucose homopolymer β-(1,3)-D-glucan is an essential component of the cell wall of many fungi.[3] Caspofungin is a semisynthetic echinocandin that inhibits the synthesis of β-(1,3)-D-glucan, thus interfering with fungal cell wall synthesis. This process of fungal cell wall synthesis has no counterpart in mammals.

### *In Vitro* Studies

Caspofungin has a broad spectrum of antifungal activity *in vitro*. However, standardised methods for the susceptibility testing of glucan synthesis inhibitors such as caspofungin have not been established and the results of susceptibility testing do not necessarily correlate with clinical outcome.[4]

• Caspofungin showed *in vitro* activity against *Aspergillus fumigatus*, *A. flavus*, *A. terreus* and *A. niger* in a study that used *Aspergillus* isolates from patients involved in clinical trials.[5] The study used a National Committee for Clinical Laboratory Standards (NCCLS) broth microdilution assay. The *in vitro* activity of caspofungin against *Aspergillus* species has also been demonstrated in other studies using NCCLS broth microdilution assays.[6-8]

• No antagonism between caspofungin and amphotericin B was seen against *A. fumigatus*, *A. flavus*, *A. niger* and *A. terreus in vitro*, although some synergistic and additive activity was observed.[9]

• *In vitro* studies have shown caspofungin to have activity against azole-sensitive and -resistant *Candida* species[4,10-19] and amphotericin-resistant *Candida* species.[20] Caspofungin has also demonstrated *in vitro* activity against several filamentous fungi besides *Aspergillus*[14,21] and several dimorphic fungi.[14] Caspofungin has demonstrated limited *in vitro* activity against *Cryptococcus neoformans*.[14,19]

### Animal Studies

#### *In Aspergillosis*

• In a survival model involving complement component 5-deficient mice with disseminated aspergillosis, the 50% effective dose was 0.06 mg/kg with once daily intraperitoneal administration of caspofungin.[22] At day 28 after intravenous challenge with *A. fumigatus*, the survival rate was ≥78% with administration of caspofungin at dosages of ≥0.16 mg/kg/day, initiated 30 minutes after challenge and continued for 5 days, while all infected control mice had died.

• Mice with transient cyclophosphamide-induced immunosuppression and disseminated aspergillosis received once daily intraperitoneal caspo-

fungin or amphotericin B 0.03 to 1 mg/kg for 14 days, starting 24 hours after infection with *A. fumigatus*.[23] Survival rates at 28 days were 70, 90, 90 and 50% in recipients of caspofungin 0.5 and 1 mg/kg/day and amphotericin B 0.5 and 1 mg/kg/day, respectively. Survival was significantly ($p \leq 0.05$) prolonged in recipients of caspofungin at dosages of ≥0.125 mg/kg/day (≥40%), compared with infected control mice, all of which died. Mice with chronic cyclophosphamide-induced immunosuppression and disseminated aspergillosis received once daily treatment with intraperitoneal caspofungin or amphotericin B 0.25 to 1 mg/kg for 7 days, starting 24 hours after infection.[23] Among mice treated with ≥0.5 mg/kg/day of caspofungin or amphotericin B, 28-day survival rates ranged from 50 to 100% and from 40 to 90%, respectively.

• Both prophylaxis and treatment with intraperitoneal caspofungin were effective in a rodent model of pulmonary aspergillosis. In the prophylaxis trial, rats received single doses of caspofungin 0.5, 2 or 8 mg/kg, amphotericin B 4 mg/kg or saline, 2 hours prior to tracheal inoculation with *A. fumigatus*.[24] Seven days after infection, survival rates were 60, 90, 100, 100 and 40% in the corresponding treatment groups. In the treatment trial, survival rates at 7 days after infection among rats that received 7 days' treatment with intraperitoneal caspofungin 0.5, 2 or 8 mg/kg once daily, amphotericin B 4 mg/kg once daily or saline were 80, 100, 100, 100 and 30%, respectively.[24]

#### *Other Pathogens*

• Caspofungin has shown efficacy in a range of murine models of fungal infection including disseminated candidiasis in immunocompetent, immunosuppressed and neutropenic hosts (including *Candida krusei* and *C. glabrata* infection[25]),[22,23,26-29] histoplasmosis[30,31] and *Pneumocystis carinii*.[32] In contrast, the drug did not protect immunodeficient mice against lethal challenge with *C. neoformans*.[22]

## 2. Pharmacokinetic Profile

### Absorption and Distribution

• The plasma caspofungin concentration increased proportionally with the dose in healthy men (n = 12) who received single intravenous infusions of 5 to 100mg.[33] Moderate accumulation [25 to 50% increase in the area under the plasma concentration-time curve ($AUC_{24h}$)] of caspofungin was seen with multiple dosing in healthy men who received intravenous caspofungin 15 to 70 mg/day for 2 weeks and in 10 healthy men who received intravenous caspofungin 70 mg/day for 3 weeks.[33] The studies were published as abstracts.

• Caspofungin is highly protein bound in human serum (approximately 96%).[34] Following intraperitoneal administration of a single dose of [$^3$H]-labelled caspofungin 1 mg/kg to mice, the tissue-to-plasma ratio for $AUC_{24h}$ was 16, 2.9 and 2 for the liver, kidney and large intestine, respectively.[34] The exposure of the small intestine, lung and spleen to caspofungin was similar to that of plasma, while the exposure of the heart, thigh and brain was lower than that of plasma.

### Metabolism and Elimination

• Caspofungin was slowly metabolised by hydrolysis and *N*-acetylation in healthy adults who received a single 1-hour intravenous infusion of [$^3$H]-labelled caspofungin 70mg.[35] Caspofungin also undergoes spontaneous chemical degradation.[36] The β-phase elimination half-life of caspofungin was 9 to 10 hours in healthy men after single intravenous infusions of 5 to 100mg.[33] An additional phase with a longer half-life was seen at higher doses. The total plasma clearance of caspofungin was 0.72 L/h.[36]

• 27 days after intravenous administration of radiolabelled caspofungin, 35% of the dose had been excreted in faeces and 41% of the dose had been excreted in urine.[36] However, ≈1.4% of the dose was excreted in the urine unchanged, suggesting that the primary route of excretion is hepatic metabolism.

Special Patient Populations

- The results of a study in healthy elderly volunteers aged >65 years, presented as a poster, indicated that the caspofungin dosage should not need to be adjusted in elderly patients, despite modestly increased plasma concentrations (11.32 and 1.57 mg/L, respectively, 1 and 24 hours after a single 70mg dose) compared with healthy volunteers aged <45 years (10.45 and 1.19 mg/L, respectively).[37]

- The caspofungin dosage does not need to be adjusted in patients with renal insufficiency or mild hepatic insufficiency, although dosage reduction is recommended in patients with moderate hepatic insufficiency.[36] The use of caspofungin in patients with severe hepatic insufficiency has not been studied.

## 3. Therapeutic Trials

There are limited clinical data regarding the use of caspofungin in patients with invasive fungal infections. This section discusses the results of 1 noncomparative study which examined the use of caspofungin in invasive aspergillosis (data presented in a poster)[38] and 2 randomised, double-blind, comparative studies which examined the use of caspofungin in mucosal candidiasis (data presented as abstracts).[39,40]

- A multicentre noncomparative study involved 56 immunocompromised patients who met the diagnostic criteria for definite or probable pulmonary invasive aspergillosis or definite extrapulmonary invasive aspergillosis.[38] 46 patients were refractory to other antifungal agents (including amphotericin B, lipid formulations of amphotericin B, itraconazole or investigational azoles) and 10 patients did not tolerate other antifungal agents. 12 patients had neutropenia at baseline (absolute neutrophil count of <500 cells/μl); the site of *Aspergillus* infection and the underlying conditions of patients are shown in figures 1 and 2, respectively. 54 patients received at least 1 dose of caspofungin; treatment comprised an intravenous loading dose of caspofungin 70mg followed by once daily intravenous caspofungin 50mg for up to 162 days (mean 31.1 days).

- Response was assessed by an independent expert panel; a complete response (defined as resolution of all attributable symptoms, signs and radiographic or bronchoscopic abnormalities) or a partial response (defined as a clinically meaningful improvement in attributable symptoms, signs and radiographic or bronchoscopic abnormalities) occurred in 22 of the 54 patients (40.7%).[38] A favourable response (defined as a complete or partial response) was seen in 34.1 and 70% of patients who were refractory to, or did not tolerate, previous antifungal therapy, respectively, and in 18.2 and 46.5% of patients who did, and did not, have neutropenia at baseline, respectively. The proportions of patients achieving a favourable response accord-

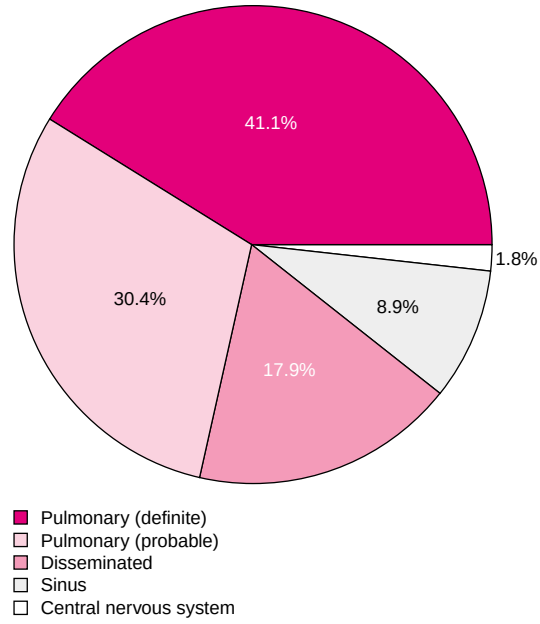



**Fig. 1.** Site of infection in patients with invasive aspergillosis. This multicentre noncomparative study involved 56 immunocompromised patients meeting the diagnostic criteria for invasive aspergillosis who were treated with caspofungin.[37]

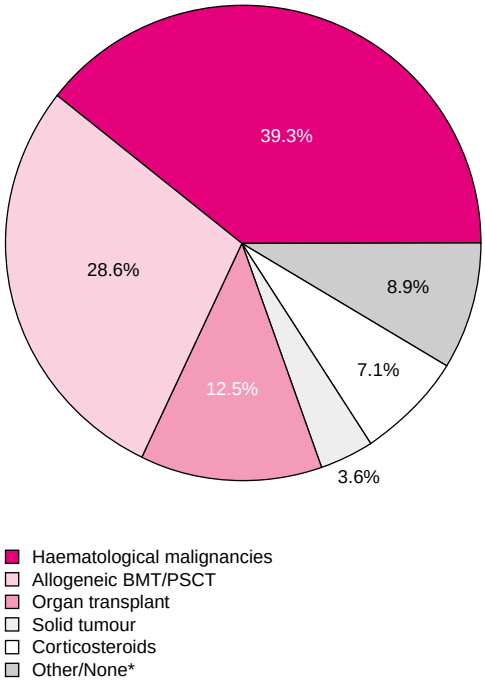



**Fig. 2.** Underlying disease in patients with invasive aspergillosis. This multicentre noncomparative study involved 56 immunocompromised patients meeting the diagnostic criteria for invasive aspergillosis who were treated with caspofungin.[37] **BMT** = bone marrow transplantation; **PSCT** = peripheral stem cell transplantation; * Other/None includes 1 methotrexate recipient, 1 patient with an underlying mycobacterial lung infection, 1 patient with skull trauma and 2 patients in whom no underlying condition was present.

ing to the underlying disease and the site of infection are shown in figure 3.

• The preliminary results of a multicentre double-blind study indicated that caspofungin is effective in oesophageal candidiasis.[39] 128 patients with endoscopically proven oesophageal candidiasis were randomised to receive intravenous caspofungin 50 or 70 mg/day, or intravenous amphotericin B 0.5 mg/kg/day, for 14 days. 78 and 82% of caspofungin and amphotericin B recipients, respectively, had HIV infection. A clinical response (defined as a resolution of symptoms and a significant reduction in endoscopic lesions 14 days after completing therapy) was seen in 38 of the 46 caspofungin 50 mg/day recipients (82.6%), 25 of the 28 caspofungin 70 mg/day recipients (89.3%) and 36 of the 54 amphotericin B recipients (66.7%).

• Caspofungin was effective in oropharyngeal and oesophageal candidiasis, according to the preliminary results of a multicentre, randomised, double-blind study involving 95 evaluable patients who received caspofungin 35, 50 or 70 mg/day, or amphotericin B 0.5 mg/kg/day.[40] Nearly all of the patients had HIV infection. The minimum duration of treatment was 7 and 10 days for patients with oropharyngeal and oesophageal candidiasis, respectively. Among patients with oropharyngeal candidiasis, treatment was deemed effective (assessed 3 to 4 days after the end of therapy and defined as complete resolution of symptoms and a reduction in disease grade to 0 or 1/2) in 78, 91 and 100% of caspofungin 35, 50 and 70 mg/day recipients, respectively, and in 83% of amphotericin B recipients. Among patients with oesophageal candidiasis, treatment was effective in 79, 93, 78 and 69% of patients in the corresponding treatment groups.

## 4. Tolerability

• Caspofungin was generally well tolerated in a multicentre noncomparative trial involving adults with invasive aspergillosis who received a loading dose of intravenous caspofungin 70mg followed by once daily intravenous caspofungin 50mg for 1 to 162 days.[38] One or more drug-related clinical adverse effects were experienced by 13.8% of patients (the most common were fever, nausea, vomiting and complications associated with the vein into which caspofungin was infused). Laboratory abnormalities related to caspofungin therapy that occurred in >1 patient included increased proteinuria (n = 3) and eosinophilia (n = 2). Pulmonary infiltrates and hypercalcaemia were the 2 serious drug-related adverse effects reported. Systemic reactions associated with the infusion of caspofungin

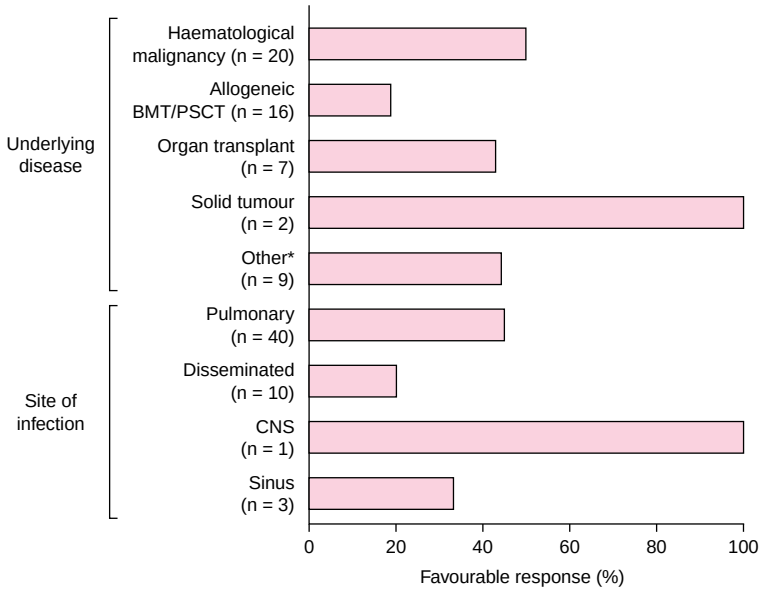



**Fig. 3.** Percentage of patients achieving a favourable response (defined as a complete or partial response) according to their underlying disease and site of infection at baseline. This multicentre noncomparative study involved 54 immunocompromised patients with invasive aspergillosis who received at least 1 dose of caspofungin.[37] **BMT** = bone marrow transplantation; **PSCT** = peripheral stem cell transplantation; **CNS** = central nervous system; * Other includes 4 corticosteroid recipients, 1 patient who received methotrexate, 1 patient with an underlying mycobacterial lung infection, 1 patient with skull trauma and 2 patients in whom no underlying condition was present.

occurred in 17% of patients, although the majority of these reactions were of mild severity.

- Drug-related laboratory adverse effects occurred with generally similar frequency in caspofungin and fluconazole recipients in a pooled analysis of data from 3 double-blind, randomised studies involving patients with mucosal *Candida* infections. The analysis included recipients of intravenous caspofungin 50mg (n = 164), caspofungin 70mg (n = 65), amphotericin B 0.5 mg/kg (n = 89) and fluconazole 200mg (n = 93).[41] Elevated creatinine levels occurred in 0, 1.5, 28.1 and 2.2% of patients in the corresponding treatment groups, elevated ALT levels occurred in 10.5, 10.8, 22.7 and 12% and elevated AST levels occurred in 13, 10.8, 22.7 and 13%; in caspofungin recipients most of the increases in hepatic enzyme levels were of a transient nature and did not limit therapy. No serious drug-related adverse effects occurred in caspofungin recipients. In total, 6 of the 263 caspofungin recipients (including 34 patients who received caspofungin 35 mg/day) discontinued therapy because of drug-related adverse effects.

- No serious adverse effects were associated with caspofungin in a multicentre, randomised, double-blind study involving 128 patients with oesophageal candidiasis.[39] One serious adverse effect was seen in amphotericin B recipients. Creatinine levels of >176.8 μmol/L (>2 mg/dl) developed in 8 amphotericin B recipients and 1 caspofungin recipient. Three of the 74 caspofungin recipients (4.1%) discontinued therapy because of drug-related adverse effects compared with 12 of the 54 amphotericin B recipients (22.2%).

### Potential Drug Interactions

- The pharmacokinetics of the recommended dosage of caspofungin (70mg on day 1 followed by 50 mg/day) were not significantly altered by coadministration of oral itraconazole 200 mg/day for 14 days and, similarly, the pharmacokinetics of itraconazole were not significantly altered by coadministration of caspofungin.[42] Studies conducted in healthy volunteers indicated that the pharmacokinetics of caspofungin were not altered by the coadministration of amphotericin B, mycophenolate mofetil or tacrolimus and, similarly, the pharmacokinetics of amphotericin B and the active metabolites of mycophenolate mofetil were not altered by coadministration of caspofungin.[36]

- Plasma concentrations and the AUC of tacrolimus were modestly reduced by about 20% with coadministration of caspofungin, and tacrolimus concentrations should be monitored in patients receiving both drugs.[36]

- Cyclosporin increased the AUC of caspofungin by about 35% although plasma concentrations of cyclosporin were not altered by coadministration of caspofungin.[36] Elevated transaminase levels were seen in a study involving healthy volunteers who received caspofungin and cyclosporin.[36] Transiently elevated ALT levels were seen on day 11 in 3 of the 4 volunteers who received caspofungin 70 mg/day on days 1 to 10 plus 2 doses of cyclosporin 3 mg/kg administered 12 hours apart on day 10; ALT levels were 2 to 3 times the upper limit of normal. In the same study, small increases in ALT levels were seen on day 2 in 2 of the 8 volunteers who received caspofungin 35 mg/day for 3 days plus 2 doses of cyclosporin 3 mg/kg administered 12 hours apart on day 1; ALT levels were slightly above the upper limit of normal. In both panels, AST levels were also elevated, but to a lesser extent than ALT levels. The concomitant use of caspofungin and cyclosporin is currently not recommended.

## 5. Caspofungin: Current Status

Caspofungin is a glucan synthesis inhibitor that has been launched in the US for the treatment of patients with invasive aspergillosis who have not responded to, or do not tolerate, conventional antifungal therapy. Studies are currently underway for the empirical treatment of febrile neutropenia, invasive candidiasis and paediatric usage.

## References


1. Chiou CC, Groll AH, Walsh TJ. New drugs and novel targets for treatment of invasive fungal infections in patients with cancer. Oncologist 2000; 5 (2): 120-35
2. De Pauw BE, Donnelly JP, Verweij PE, et al. Current management of fungal infections in immunocompromised patients and polyene lipid complexes for treatment of invasive fungal infection. J Infect Dis Antimicrob Agents 1998 May-Aug; 15: 85-96
3. Maertens JA, Boogaerts MA. Fungal cell wall inhibitors: Emphasis on clinical aspects. Current Pharmaceutical Design 2000; 6 (2): 225-39
4. Scott Hicks P, Dorso K, Gerckens L, et al. Comparative in vitro susceptibility of clinical trial isolates to the glucan synthesis inhibitor antifungal caspofungin (Cancidas™, MK-0991) [abstract]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 18; Toronto
5. Flattery AM, Scott Hicks P, Wilcox A, et al. In vitro susceptibility of clinical trial isolates of *Aspergillus* spp. to the glucan synthesis inhibitor caspofungin acetate (Cancidas™, MK-0991) [poster]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 18; Toronto
6. Espinel-Ingroff A. Comparison of in vitro activities of the new triazole SCH56592 and the echinocandins MK-0991 (L-743,872) and LY303366 against opportunistic filamentous and dimorphic fungi and yeasts. J Clin Microbiol 1998 Oct; 36: 2950-6
7. Arikan S, Lozano-Chiu M, Paetznick V, et al. *In vitro* susceptibility testing methods for caspofungin against *Aspergillus* and *Fusarium* isolates [abstract]. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 26: 546
8. Pfaller MA, Marco F, Messer SA, et al. *In vitro* activity of two echinocandin derivatives, LY303366 and MK-0991 (L-743,792), against clinical isolates of *Aspergillus*, *Fusarium*, *Rhizopus*, and other filamentous fungi. Diagn Microbiol Infect Dis 1998 Apr; 30: 251-5
9. Arikan S, Lozano-Chiu M, Paetznick V, et al. *In vitro* synergy studies with caspofungin and amphotericin B against *Aspergillus* and *Fusarium* [abstract]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 18; Toronto, 368
10. Barchiesi F, Schimizzi AM, Fothergill AW, et al. *In vitro* activity of the new echinocandin antifungal, MK-0991, against

common and uncommon clinical isolates of *Candida* species. Eur J Clin Microbiol Infect Dis 1999 Apr; 18: 302-4
11. Bachmann SP, Perea S, Kirkpatrick WR, et al. *In vitro* activity of Cancidas (MK-0991) against *Candida albicans* clinical isolates displaying different mechanisms of azole resistance [abstract]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 18; Toronto, 352
12. Cohen S, Carroll K. *In vitro* evaluation of pneumocandin activity against clinical isolates of yeasts [abstract]. 99th General Meeting American Society for Microbiology; 1999 May 30, 138
13. Marco F, Pfaller MA, Messer SA, et al. Activity of MK-0991 (L-743,872), a new echinocandin, compared with those of LY303366 and four other antifungal agents tested against blood stream isolates of Candida spp. Diagn Microbiol Infect Dis 1998 Sep; 32: 33-7
14. Espinel-Ingroff A. *In vitro* studies with L-743,872, a water soluble pneumocandin: a comparative study [abstract]. 36th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1996 Sep 15-18; New Orleans, 105
15. Vazquez JA, Lynch M, Boikov D, et al. *In vitro* activity of a new pneumocandin antifungal, L-743,872, against azole-susceptible and -resistant *Candida* species. Antimicrob Agents Chemother 1997 Jul; 41: 1612-4
16. Vazquez JA, Boikov D, Lynch ME, et al. *In-vitro* antifungal activity of L-743,872, a new penumocandin, against sensitive and resistant Torulopsis and Candida species [abstract]. 36th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1996 Sep 15-18; New Orleans, 105
17. Scott PM, Gerckens L, Lynch L, et al. Comparative *in vitro* susceptibility of clinical trial isolates to the echinocandin antifungal MK-991 [abstract]. 38th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1998 Sep 25-27; San Diego, 452
18. Pfaller MA, Messer SA, Gee S, et al. *In vitro* susceptibilities of *Candida dubliniensis* isolates tested against the new triazole and echinocandin antifungal agents. J Clin Microbiol 1999 Mar; 37: 870-2
19. Krishnarao TV, Galgiani JN. Comparison of the in vitro activities of the echinocandin LY303366, the pneumocandin MK-0991, and fluconazole against *Candida* species and *Cryptococcus neoformans*. Antimicrob Agents Chemother 1997 Sep; 41: 1957-60
20. Nelson PW, Lozano-Chiu M, Rex JH. *In vitro* growth-inhibitory activity of pneumocandins L-733,560 and L-743,872 against putatively amphotericin B- and fluconazole-resistant Candida isolates: influence of assay conditions. J Med Vet Mycol 1997 Jul-Aug; 35: 285-7
21. Del-Poeta M, Schell WA, Perfect JR. In vitro antifungal activity of pneumocandin L-743,872 against a variety of clinically important molds. Antimicrob Agents Chemother 1997 Aug; 41: 1835-6
22. Abruzzo GK, Flattery AM, Gill CJ, et al. Evaluation of the echinocandin antifungal MK-0991 (L-743,872): efficacies in mouse models of disseminated aspergillosis, candidiasis, and cryptococcosis. Antimicrob Agents Chemother 1997 Nov; 41: 2333-8
23. Abruzzo GK, Gill CJ, Flattery AM, et al. Efficacy of the echinocandin caspofungin against disseminated aspergillosis and candidiasis in cyclophosphamide-induced immunosuppressed mice. Antimicrob Agents Chemother 2000 Sep; 44: 2310-8
24. Bernard EM, Ishimaru T, Armstrong D. Low doses of the pneumocandin, L-743,872, are effective for prevention and treatment in an animal model of pulmonary aspergillosis [abstract]. 36th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1996 Sep 15-18; New Orleans, 106
25. Graybill JR, Bocanegra R, Luther M, et al. Treatment of murine *Candida krusei* or *Candida glabrata* infection with L-743,872. Antimicrob Agents Chemother 1997 Sep; 41: 1937-9
26. Graybill JR, Najvar LK, Luther MF, et al. Treatment of murine disseminated candidiasis with L-743,872. Antimicrob Agents Chemother 1997 Aug; 41: 1775-7
27. Flattery AM, Abruzzo GK, Smith JG, et al. Activity of pneumocandin L-743872 in a CD4+ T-cell deficient mouse model of oropharyngeal and gastrointestinal candidiasis [abstract]. 36th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1996 Sep 15-18; New Orleans, 106
28. Smith JG, Abruzzo GK, Gill CJ, et al. Evaluation of pneumocandin L-743872 in neutropenic mouse models of disseminated candidiasis and aspergillosis [abstract]. 36th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1996 Sep 15-18; New Orleans, 107
29. Bartizal K, Smith JG, Gill CJ, et al. Preclinical efficacy of MK-0991 in pancytopenic mouse models of disseminated candidiasis and aspergillosis [abstract]. 37th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1997 Sep 28; Toronto, 159
30. Graybill JR, Najvar LK, Montalbo EM, et al. Treatment of histoplasmosis with MK-991 (L-743,872). Antimicrob Agents Chemother 1998 Jan; 42: 151-3
31. Kohler S, Wheat LJ, Connolly P, et al. Comparison of the echinocandin caspofungin with amphotericin B for treatment of histoplasmosis following pulmonary challenge in a murine model. Antimicrob Agents Chemother 2000 Jul; 44: 1850-4
32. Powles MA, Liberator P, Anderson J, et al. Efficacy of MK-991 (L-743,872), a semisynthetic pneumocandin, in murine models of *Pneumocystis carinii*. Antimicrob Agents Chemother 1998 Aug; 42: 1985-9
33. Stone JA, Holland SD, Ju WD, et al. Single- and multiple-dose pharmacokinetics of the antifungal agent MK-0991 in man [abstract]. 38th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1998 Sep 25-27; San Diego, 83
34. Hajdu R, Thompson R, Sundelof JG, et al. Preliminary animal pharmacokinetics of the parenteral antifungal agent MK-0991 (L-743,872). Antimicrob Agents Chemother 1997 Nov; 41: 2339-44
35. Balani SK, Xu X, Arison BH, et al. Metabolites of caspofungin acetate, a potent antifungal agent, in human plasma and urine. Drug Metab Dispos 2000 Nov; 28: 1274-8
36. Merck & Co. Cancidas® (caspofungin acetate) prescribing information. Merck & Co. Available from: URL: http://www.merck.com [Accessed 2001 Mar 16]
37. Stone JA, Ballow CH, Holland S, et al. Single dose caspofungin pharmacokinetics in healthy elderly subjects [poster]. 40th

Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 18, Toronto
38. Maertens J, Raad I, Sable CA, et al. Multicenter, noncomparative study to evaluate safety and efficacy of caspofungin (CAS) in adults with invasive aspergillosis (IA) refractory or intolerant (I) to amphotericin B (AMB), AMB lipid formulations (lipid AMB), or azoles [poster]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 18; Toronto
39. Sable CA, Villanueva A, Arathon E, et al. A randomized, double-blind, multicenter trial of MK-991 vs. amphotericin B in the treatment of Candida esophagitis in adults [abstract]. 37th Interscience Conference on Antimicrobial Agents and Chemotherapy1997 Sep 28-Oct 1; Toronto, 15
40. Arathoon E, Gotuzzo E, Noriega L, et al. A randomized, double-blind, multicenter trial of MK-0991, an echinocandin antifungal agent, vs amphotericin B for the treatment of oropharyngeal and esophageal candidiasis in adults [abstract]. Clin Infect Dis 1998 Oct; 27: 939
41. Sable CA, Nguyen BY, Chodakewitz JA, et al. Safety of caspofungin acetate (CA) in the treatment of fungal infections [poster]. Focus on Fungal Infections 11; 2001 Mar 14-16; Washington DC
42. Stone JA, McCrea J, Wickersham P, et al. A phase I study of caspofungin evaluating the potential for drug interactions with itraconazole, the effect of gender and the use of a loading dose regimen [poster]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 18; Toronto

Correspondence: *Gillian M. Keating*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand.
E-mail: demail@adis.co.nz