Emerging Drug List
Caspofungin Acetate

Canadian Coordinating Office for Health Technology Assessment

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Generic (Trade Name)**:** Caspofungin acetate (Candicas®)

Manufacturer: Merck Frosst Canada & Co.

Indication: For the treatment of invasive aspergillosis in patients who fail to respond to, or are unable to tolerate, other antifungal drugs, including amphotericin B and itraconazole.

Current Regulatory Status: Caspofungin acetate received FDA approval and was launched in the United States in February 2001 for the above indication. Caspofungin has received a Notice of Compliance from Health Canada, dated July 17, 2001. Currently, its launch in Canada is anticipated for September 2001.

Description: Caspofungin is a novel antifungal agent of the echinocandin class. It exerts its activity by noncompetitively inhibiting the synthesis of an integral component of fungal cell walls, namely beta-(1,3)-D glucan. *In vitro*, caspofungin exhibits a wide range of activity against many pathogens, including Aspergillus (e.g., *A. flavus, A. niger, A fumigatus)* and Candida (e.g., *C. albicans, C. glabrata, C. tropicalis*). However, *in vitro*, it does not possess appreciable activity against *C. neoformans.*

Caspofungin has negligible bioavailability when administered orally; therefore parenteral dosing is indicated. After administration, caspofungin is extensively albumin-bound (97%) and distributes to tissues. The drug is slowly eliminated, showing triphasic elimination; half lives can be quantified as 1-2 hours, 9-11 hours and 40-50 hours. The cytochrome p450 system is not appreciably involved in the metabolism of caspofungin; peptide hydrolysis and N-acetylation likely account for caspofungin's metabolism with a small percentage being retrieved in the urine. For the approved indication, caspofungin is administered as a 70 mg loading dose (over one hour) on the first day of therapy, followed by 50 mg daily, or 35 mg per day in the case of a patient with moderate hepatic insufficiency.

Current Existing Treatments: According to the Sanford Guide®, treatment of invasive aspergillosis consists of parenteral amphotericin B (Fungizone® - Squibb) or iv/po itraconazole (Sporanox® - Janssen-Ortho). The parenteral version of Sporonox® may be obtained only via the Special Access Program. Alternate therapy includes lipid formulations of amphotericin B (e.g., Albecet® Lipid Complex Injection - The Liposome Company, Ambisome® for Injection - Fujisawa). Other agents are currently under various stages of investigation to determine their aptitude to treat fungal infections, including aspergillosis (e.g., voriconazole, LY303366, FK463, SCH56592, BMS207147, nikkomycin Z, liposomal nystatin).

Cost: The Canadian cost of this product is not available at this time. The cost in US$ for the 50 and 70 mg vials is approximately $288 and $371, respectively. One review article cites that a typical treatment cycle (50 mg daily for 34 days) would cost $US 9,875.

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Evidence: To date, clinical trials describing the efficacy of caspofungin are sparse. Published studies typically describe animal testing or *in vitro* susceptibility data. However, there has been some work published in abstract format or presented at conferences.

One trial, conducted in a noncomparative, open-label, multicentre format, examined the efficacy of caspofungin in its approved indication. Patients (n=63) with *Aspergillus* infections who were either intolerant of (10/63) or refractory to (53/63) treatment (at least seven days) with typical antifungals received a 70 mg dose intravenously, followed by 50 mg daily. Duration of treatment ranged from one to 162 days, with a mean of 33.7 days. A favorable response rate, defined as complete resolution or clinical improvement, was apparent in 41.3% of patients overall, or 35.8 and 70% of those that were previously resistant or intolerant of therapy, respectively. If segregated into site of infection, response was evident in 46.7% of those with pulmonary infection, and 27.8% for those with infection at other sites. Overall, therapy was well tolerated, with a discontinuance rate of 5.2% owing to untoward effects. Two reactions "possibly" related to the medication were deemed serious, one case of hypercalcemia and another of a pulmonary infiltrate.

The efficacy of caspofungin in treating candidal esophagitis has also been described. Patients (n=128) were randomized in a double-blind fashion to receive 14 days of therapy with either caspofungin (50 or 70 mg daily) or amphotericin B (0.5 mg/kg/day). Patients with HIV accounted for the majority of enrolled patients, approximately 80%. A resolution of symptoms with a significant reduction in endoscopic lesions (two weeks after stopping treatment) was noted in 82.6, 89.3 and 66.7% of those patients who received caspofungin low and high dose, or amphotericin B, respectively (p values not reported). Although details were not provided, it was stated that adverse effects that could be attributed to the medication were less frequent in those treated with caspofungin.

Clinical trials are still ongoing to assess the efficacy of caspofungin as empiric therapy in febrile neutropenia, for the treatment of esophageal candidiasis (vs. fluconazole) and invasive candidiasis.

Adverse Effects: Fever, infusion site reactions, nausea, vomiting, flushing, increased alkaline phosphatase, decreased potassium, increased eosinophils, increased urine protein and RBCs have been reported in patients being treated for aspergillosis. Serum creatinine elevations were reported infrequently. An interaction between caspofungin and cyclosporine, causing a 35% increase in AUC of the former, has been observed. Also, an elevation in liver function tests were noted more frequently when this combination was used. Further studies are underway to determine the potential for interaction with caspofungin.

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Conclusion: Invasive aspergillosis is a troublesome disease to treat, particularly as most patients have some degree of immunosuppression. Aggressive, early management with antimycotic medication is required to minimize morbidity and mortality. Caspofungin is currently indicated for patients refractory to, or intolerant of standard treatment, serving as an alternate therapeutic avenue where the options are currently limited. At this time, published data is scant; clinical trials, published in full, are required to assess the true benefits and role of this medication. The evidence to date alludes to a differing adverse effect profile from the gold standard amphotericin b (i.e., nephrotoxicity versus hepatotoxicity). What will be interesting to elucidate is how this product compares when used as primary therapy versus standard agents in a broader range of fungal diseases, and which patients are better served by individualizing therapy with a specific antifungal.

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