CEDAC FINAL RECOMMENDATION on RECONSIDERATION and REASONS for RECOMMENDATION

VORICONAZOLE RESUBMISSION
(Vfend™ - Pfizer Canada Inc.)

Description:
Voriconazole is a triazole antifungal agent which is indicated for the treatment of invasive aspergillosis, in candidemia in non-neutropenic patients, in disseminated infections in skin due to *Candida* and in infections of the abdomen, kidney, bladder wall and wounds due to *Candida*.

The Committee previously issued a formulary listing recommendation on the use of voriconazole in invasive aspergillosis; this resubmission focused solely on the use of voriconazole in *Candida* infections.

Dosage Forms:
50 mg and 200 mg tablets and 200 mg vial for intravenous injection

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that voriconazole be listed for culture proven invasive candidiasis with documented resistance to fluconazole.

Reasons for the Recommendation:
1. The Committee considered the results of one open-labelled randomized controlled trial (RCT) comparing voriconazole with conventional amphotericin B followed by fluconazole in patients with candidemia and clinical findings consistent with infection. The primary endpoint, which was to demonstrate that voriconazole was non-inferior to amphotericin B followed by fluconazole in terms of response to therapy at 12 weeks after drug discontinuation, was achieved in 41% of voriconazole patients versus 41% of amphotericin B/fluconazole patients. There was no statistically significant difference in the duration of hospitalization between the two groups: 28 ± 26 days in the voriconazole versus 30 ± 27 days in the amphotericin B/fluconazole group.

2. Voriconazole has activity against a wide variety of *Candida* species, including non-albicans species that are resistant to fluconazole (eg. *Candida krusei*) and is an alternative to amphotericin B in serious infections due to these organisms.

3. In the RCT reviewed by the Committee, the incidence of serious adverse effects was significantly less but the incidence of withdrawals due to adverse events was significantly greater in the voriconazole treated group. However, withdrawals due to adverse events in the amphotericin B group may be underestimated since patients in this group could be switched to fluconazole without being classified

as a withdrawal due to adverse events. The adverse events that most commonly led to discontinuation of voriconazole were elevated liver function tests, rash and visual disturbances.

4. Voriconazole costs approximately $300 per day for intravenous therapy and $98 per day for oral therapy. In comparison, fluconazole 400 mg daily is $73 per day for intravenous therapy and $35 per day for oral therapy. The economic model submitted by the manufacturer reported that the average drug cost of treatment with voriconazole was $6,077 versus $1,468 for amphotericin B/fluconazole. The model reported that this cost difference was largely offset by a reduction in the cost of one less day of intensive care unit stay with voriconazole, but there was no statistically significant difference in duration of intensive care unit stay in favour of voriconazole in the RCT. Therefore, the Committee felt that the increased cost of voriconazole could only be justified in patients with invasive candidiasis with documented resistance to fluconazole.

Of Note:

1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.

2. Voriconazole is an alternative to amphotericin B in patients for whom oral therapy would be preferable to intravenous therapy in an outpatient setting.