CEDAC FINAL RECOMMENDATION on RECONSIDERATION and REASONS for RECOMMENDATION

POSACONAZOLE
(Spriafil™ – Schering–Plough Canada Inc.)

Description:
Posaconazole is a triazole antifungal agent that is approved for use in patients 13 years of age and older for:

- prophylaxis of *Aspergillus* and *Candida* infections in patients at high risk of developing these infections, such as patients with prolonged neutropenia or hematopoietic stem cell transplant (HSCT) recipients;
- treatment of invasive aspergillosis in patients refractory to amphotericin B or itraconazole, or in patients who are intolerant of these agents;
- treatment of oropharyngeal candidiasis.

Dosage Forms:
40 mg/mL oral suspension.

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that posaconazole not be listed.

Reasons for the Recommendation:
The Committee considered each of the three approved indications for posaconazole separately.

Prophylaxis of Aspergillus and Candida Infections

1. Posaconazole is more effective than fluconazole in reducing the incidence of proven/probable invasive *Aspergillus* infections in high risk, severely neutropenic patients. This is not unexpected given the lack of activity of fluconazole against *Aspergillus*. There is insufficient evidence comparing posaconazole with other, less expensive antifungal drugs active against *Aspergillus*.

2. Posaconazole and fluconazole have similar efficacy in preventing *Candida* infections in high risk, severely neutropenic patients.

3. Posaconazole costs $141 per day at the dose recommended for use in the prophylaxis of fungal infections (200 mg three times daily), which is significantly more than other oral antifungal agents.

Treatment of Invasive Aspergillosis

1. The evidence in support of the use of posaconazole in the treatment of invasive aspergillosis consists of a trial with a historical control population, while the efficacy of other agents for this indication have been established by randomized controlled trials (RCTs). The Committee felt that this was

insufficient evidence to determine the efficacy of posaconazole and therefore its appropriate place in therapy.

2. Posaconazole costs $188 per day at the dose recommended for use in the treatment of invasive aspergillosis (800 mg per day in two or four divided doses), which is significantly more than voriconazole ($190 per day for the first day of therapy followed by $95 per day for the remainder of therapy) and itraconazole ($16 to $35 per day).

Treatment of Oropharyngeal Candidiasis

1. One RCT reported that posaconazole had similar efficacy to fluconazole in the treatment of oropharyngeal candidiasis. However, the cost of treatment for this indication is significantly more for posaconazole compared with fluconazole ($359 vs $62 for 14 days of treatment).

Summary of Committee Considerations:

Prophylaxis of Aspergillus and Candida Infections

The Committee considered a systematic review of RCTs evaluating posaconazole in patients at high risk of developing systemic fungal infections. Two trials of posaconazole used for prophylaxis met the inclusion criteria for the systematic review. One unblinded trial of 602 patients compared posaconazole (n=304) with either fluconazole (n=240) or itraconazole (n=58), chosen at the discretion of the study site investigator, in patients with chemotherapy-induced neutropenia. There were too few patients randomized to itraconazole to allow for meaningful comparison between posaconazole and itraconazole. The other trial was a double-blind comparison of posaconazole with fluconazole in 600 patients who had undergone HSCT and had graft-versus-host disease (GVHD). Both trials reported statistically significant improvements with posaconazole for the prevention of invasive aspergillosis (number needed to treat of 17 to 21). Only the unblinded trial reported that posaconazole resulted in statistically significant reductions in the incidence of probable/proven invasive fungal infections and all cause mortality.

The manufacturer submitted an economic evaluation for this indication which assumed that patients treated with posaconazole would have a lower risk of developing fungal infections and therefore a reduced duration of hospitalization (and lower costs) compared to fluconazole. Given the concerns about treatment efficacy noted above (including the issues with respect to the appropriate comparator) and the fact that the duration of hospitalization was not measured in the clinical trials, the committee felt that the use of posaconazole for this indication had not been demonstrated to be cost-effective.

Treatment of Invasive Aspergillosis

The Committee considered a systematic review of controlled and uncontrolled trials evaluating posaconazole in the treatment of patients with invasive aspergillosis refractory to or intolerant of conventional antifungal therapy. One nonrandomized trial reported on the use of posaconazole in a subgroup of 107 patients with probable invasive aspergillosis, from a total population of 330 patients exposed to posaconazole, and compared them with 86 patients matched from a historical cohort. The primary outcome of the study, global response at the end of therapy adjudicated by a blinded data review committee, was achieved in 42% of posaconazole patients compared with 26% of controls, a statistically significant difference. However, most of this difference in efficacy was due to a difference in partial response (36% vs 16% respectively) as opposed to complete response (7% vs 9% respectively). The nonrandomized trial design, variety of treatments used in the control group and potential bias with the use of a retrospective control group makes it difficult to determine the true relative efficacy of posaconazole.

Treatment of Oropharyngeal Candidiasis
The Committee considered a systematic review of RCTs evaluating posaconazole in oropharyngeal candidiasis. One RCT comparing posaconazole with fluconazole met the inclusion criteria for the systematic review and this trial demonstrated similar efficacy for posaconazole and fluconazole.

Posaconazole is a cytochrome P450 (CYP3A4) inhibitor and has the potential for a number of serious drug interactions which require careful monitoring and management if these drugs are used concomitantly with posaconazole.

Of Note:

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

Background:

CEDAC provides formulary listing recommendations to publicly funded drug plans. Recommendations are based on an evidence-based review of the medication's effectiveness and safety and an assessment of its cost-effectiveness in comparison to other available treatment options. For example, if a new medication is more expensive than other treatments, the Committee considers whether any advantages of the new medication justify the higher price. If the recommendation is not to list a drug, the Committee has concerns regarding the balance between benefit and harm for the medication, and/or concerns about whether the medication provides good value for public drug plans.