CEDAC FINAL RECOMMENDATION on RECONSIDERATION and REASONS for RECOMMENDATION

SORAFENIB
(Nexavar® – Bayer Inc.)

Description:
Sorafenib is a multi-kinase inhibitor that has received a Notice of Compliance with Conditions (NOC/c) from Health Canada for the treatment of locally advanced/metastatic renal cell (clear cell) carcinoma in patients who have failed prior cytokine therapy or are considered unsuitable for such therapy.

Dosage Forms:
200 mg tablet. The recommended dose of sorafenib is 400 mg taken twice daily.

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

Reasons for the Recommendation:
1. Sorafenib costs $5,250 for one month of therapy. The economic evaluation submitted by the manufacturer reported an incremental cost-effectiveness of sorafenib, in addition to best supportive care, of $36,000 per life year gained (LYG), based on the assumption that sorafenib results in an overall survival advantage of 1.2 years compared to best supportive care in patients with advanced renal cell carcinoma. However, the most recent interim analysis of the pivotal randomized controlled trial (RCT) reports a non-statistically significant overall survival difference in favour of sorafenib of 5 months. Using the economic evaluation submitted by the manufacturer adjusted for an overall survival advantage of sorafenib of 4.5 months over a lifetime time horizon, the incremental cost-effectiveness of sorafenib becomes less attractive at approximately $78,000 per LYG. The incremental cost-effectiveness is also highly dependent on whether patients discontinue sorafenib therapy after disease progression. Therefore, the overall survival advantage and true cost-effectiveness of sorafenib are uncertain.

Summary of Committee Considerations:
The Committee considered a systematic review which included two RCTs in adult patients with locally advanced/metastatic renal cell carcinoma. The focus of the review was a placebo-controlled RCT in 903 patients with advanced renal cell carcinoma in which the primary endpoint was overall survival. A planned interim analysis of progression-free survival showed a statistically significant advantage in favour of sorafenib and the trial was unblinded and a large number of patients receiving placebo crossed over to sorafenib. The final overall survival data from this study are not expected until April 2007 but these results will be influenced by the cross over from placebo to sorafenib. The Health Canada approval

of sorafenib was based on promising information from the interim analyses of this trial and the NOC/c status was granted pending further verification of the benefits of sorafenib. The Committee considered the most recent interim analysis of this trial, which reported that patients treated with sorafenib had a median overall survival of 19.3 months versus 14.3 months in those who received placebo, but this difference did not meet the pre-specified threshold for statistical significance. A complete response (disappearance of all lesions) was reported in 1/451 sorafenib patients and 0/452 placebo patients. There were no statistically significant differences reported in quality of life measures for patients receiving sorafenib vs placebo. Compared to placebo, sorafenib resulted in statistically significant increases in median progression free survival (167 vs 84 days) and median time to progression (168 vs 84 days). However, in renal cell carcinoma it is uncertain if these are valid surrogate endpoints for overall survival.

Significant adverse effects of sorafenib include hypertension, hemorrhage and cardiac ischemia/infarction and there were statistically significantly more serious adverse events with sorafenib compared with placebo. Additional common adverse effects associated with sorafenib therapy are rash, hand-foot skin reactions, diarrhea and fatigue.

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.