CEDAC FINAL RECOMMENDATION on RECONSIDERATION and REASONS for RECOMMENDATION

DELTA-9-TETRAHYDROCANNABINOL (THC)/CANNABIDIOL (Sativex® – Bayer Inc.)

Description:
Delta-9-tetrahydrocannabinol (THC)/cannabidiol is a cannabinoid extract that has received a Notice of Compliance with Conditions (NOC/c) from Health Canada as adjunctive treatment for the symptomatic relief of neuropathic pain in multiple sclerosis in adults.

Dosage Forms:
Sativex® is available in a 5.5 mL vial for buccal administration by spray, containing THC 27 mg/mL and cannabidiol 25 mg/mL. The recommended dose is a maximum of one spray every four hours on the first day, up to a maximum of four sprays on the first day. On subsequent days the patient may gradually increase the total number of sprays as needed and tolerated.

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

Reasons for the Recommendation:
1. The efficacy of THC/cannabidiol in patients with multiple sclerosis has been evaluated in one small, short-term randomized controlled trial (RCT), which reported that THC/cannabidiol use resulted in a statistically significant, but clinically modest, improvement in pain relief compared to placebo.

2. THC/cannabidiol costs $136.11 per vial which contains up to 51 metered sprays. In the clinical trial evaluated by the Committee, the mean dose was 9.6 sprays per day which would cost $25.62 per day. This is more costly than other agents used to manage neuropathic pain in multiple sclerosis.

Summary of Committee Considerations:
The Committee considered a systematic review of double-blind RCTs evaluating the effect of THC/cannabidiol in adult patients with neuropathic pain associated with multiple sclerosis. One RCT of four weeks duration in 66 patients which compared THC/cannabidiol with placebo met the inclusion criteria for the systematic review. This trial was designed to detect a between-group difference of 1.75 on an 11 point numerical rating scale (NRS-11) for pain. THC/cannabidiol reduced NRS-11 pain scores from baseline by 2.7 points (a relative 42% reduction) compared to a reduction of 1.4 points (a relative 23% reduction) with placebo, a statistically significant difference. THC/cannabidiol use was also associated with statistically significant improvements in neuropathic pain scale scores and sleep disturbances, but

there were no statistically significant differences in patient global impression of change, multiple sclerosis functional status, Guy's Neurological Disability Score and neuropsychological tests.

There were no serious adverse events in patients receiving THC/cannabidiol or placebo in the RCT. Numerically more patients receiving THC/cannabidiol reported an adverse event, most commonly dizziness.

The manufacturer submitted an economic evaluation which reported that THC/cannabidiol in addition to standard analgesics, resulted in an incremental cost-effectiveness of $70,100 per quality adjusted life years (QALY) compared to standard analgesics alone. However, this evaluation assumed that the treatment benefit from a four week RCT could be extrapolated to the one year time horizon of the economic evaluation and that the difference in NRS-11 scores would translate into improved overall quality of life (ie. utility scores). The Committee felt that until these assumptions are validated by further clinical trial data, the true cost-effectiveness of THC/cannabidiol is uncertain.

The Committee also considered six additional placebo controlled RCTs of THC/cannabidiol in patients with multiple sclerosis that did not meet the criteria for the systematic review as all patients did not have neuropathic pain. Only one of these trials demonstrated that THC/cannabidiol provided better pain relief than placebo.

Of Note:

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

2. THC/cannabidiol (Sativex®) has received a NOC/c on the basis of promising clinical evidence while recognizing the need for confirmatory studies to verify its clinical benefits. The manufacturer may file a resubmission to the Common Drug Review when these confirmatory studies are completed.

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.