CEDAC FINAL RECOMMENDATION and REASONS for RECOMMENDATION

DULOXETINE
(Cymbalta™ – Eli Lilly Canada Inc.)

Description:
Duloxetine is a serotonin and norepinephrine reuptake inhibitor (SNRI) approved for the symptomatic relief of major depressive disorder in adults. Duloxetine is also approved for the management of neuropathic pain associated with diabetic peripheral neuropathy. This submission to the Common Drug Review (CDR) deals only with its use in major depressive disorder.

Dosage Forms:
30 mg and 60 mg delayed-release capsules. The recommended dose for depression is 60 mg daily.

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that duloxetine not be listed for the treatment of major depressive disorder.

Reasons for the Recommendation:

1. There is insufficient evidence that duloxetine, a selective SNRI, offers a therapeutic advantage over less expensive selective serotonin reuptake inhibitors (SSRIs). Generic SSRIs (eg. fluoxetine, paroxetine, sertraline) cost $0.63 - $1.60 per day, which is less expensive than duloxetine. The manufacturer has requested that the price of duloxetine submitted to the CDR for major depressive disorder remain confidential, pursuant to the CDR Confidentiality Guidelines.

2. The Committee considered whether duloxetine should be listed as a second-line agent after failure of an SSRI. However, there is insufficient evidence from randomized controlled trials (RCTs) that duloxetine is more effective than less expensive alternatives in patients who have failed therapy with other antidepressant agents.

Summary of Committee Considerations:

The Committee considered a systematic review of double-blind RCTs of duloxetine alone or in combination with other antidepressants in adult patients with depression. Thirteen trials in a total of 4,644 patients met the inclusion criteria for the systematic review. Nine trials were placebo-controlled and active comparators were included in seven trials (venlafaxine - one trial, escitalopram - three trials, paroxetine – three trials). Treatment duration in the active comparator trials was most commonly eight weeks (five trials), with the longest duration being 24 weeks. The 17-item Hamilton Rating Scale for Depression ($HAMD_{17}$) and the Montgomery-Asberg Depression Rating Scale were the two most frequently used scales to assess outcome.

Duloxetine was statistically significantly more effective than placebo in achieving remission (defined by a $HAMD_{17}$ score of ≤ 7) and response (defined by a $\geq 50\%$ reduction in $HAMD_{17 \text{ or } 24}$) but was not statistically significantly different from any of the active comparators. There was no significant difference in measures of quality of life between duloxetine and active treatments in the five active-comparator trials that included this outcome.

No significant differences were reported between duloxetine and any active comparators in the incidence of serious adverse events. Pooled analyses demonstrated that duloxetine-treated patients were statistically significantly more likely to withdraw from the trials or experience withdrawal due to adverse events compared to either venlafaxine or escitalopram.

The daily cost of duloxetine 60 mg is similar to venlafaxine but is more expensive than most SSRIs.

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.