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 management of diabetic peripheral neuropathic pain. Duloxetine is also approved for the symptomatic relief of major depressive disorder. This submission to the Common Drug Review relates solely to its use in diabetic peripheral neuropathic pain.

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

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that duloxetine be listed for the treatment of neuropathic pain in diabetic patients who are unresponsive to two adequate courses of less costly alternative agents such as a tricyclic antidepressant agent or an anticonvulsant agent. The dose of duloxetine should be limited to a maximum of 60 mg daily.

Reasons for the Recommendation:
1. Duloxetine 60 mg daily produced statistically and clinically significant improvements in pain rating scales and quality of life measurements compared to placebo.

2. The lack of randomized controlled trials (RCTs) comparing duloxetine to any other therapy makes it difficult to determine its place in therapy compared to less expensive alternative agents effective for the treatment of diabetic peripheral neuropathic pain such as selected tricyclic antidepressant and anticonvulsant agents.

3. There is insufficient evidence from RCTs that duloxetine 60 mg twice daily is more efficacious than duloxetine 60 mg daily, and there were numerically higher rates of withdrawals due to adverse events in patients who received 60 mg twice daily.

Summary of Committee Considerations:
The Committee considered a systematic review of double-blind RCTs evaluating the effects of duloxetine, alone or in combination with other agents for diabetic peripheral neuropathic pain, in adult patients without concomitant depression. Three 12-week RCTs comparing duloxetine to

placebo in a total of 1,139 patients were included in the systematic review. The primary outcome of all trials was reduction in the weekly mean of the 24-hour average pain scores measured by an 11-point numerical rating scale. Response at endpoint was defined as a ≥ 30% reduction from baseline on the 24-hour average pain score. Functional status and quality of life assessment, patient global impression of improvement at endpoint and clinician's impression of the severity of illness were also assessed.

Duloxetine was statistically significantly more effective than placebo in reducing the baseline 24-hour average pain scores. The number needed to treat to achieve a 30% and 50% reduction in the baseline 24-hour average pain scores with duloxetine 60 mg daily was five and six, respectively. Consistent with improvements in these primary outcomes measures, there were also improvements in several measures of quality of life for duloxetine compared with placebo.

The most common adverse events reported in duloxetine-treated patients were somnolence and nausea. Long-term safety data of duloxetine in the management of diabetic peripheral neuropathic pain beyond 12 weeks has not been assessed in controlled trials.

The manufacturer conducted a cost-effectiveness/cost-utility analysis but given the lack of direct comparative clinical evidence, the Committee felt there was significant uncertainty in this analysis. As such, the Committee considered a price comparison to other agents used in the treatment of diabetic peripheral neuropathic pain. The daily cost of duloxetine ($3.56 for 60 mg) is comparable to generic gabapentin 2400 mg daily ($3.48) but is higher than generic amitriptyline, carbamazepine and many opioid agents. At a maximum daily dose of 60 mg twice daily, duloxetine costs $7.12, which is more costly than alternative agents.

Of Note:

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

2. Duloxetine is the first SNRI agent approved for the treatment of diabetic peripheral neuropathic pain. Systematic reviews have shown that tricyclic antidepressants and anticonvulsants such as carbamazepine are also effective in patients with diabetic neuropathic pain when compared to placebo.

3. As duloxetine is also approved for the treatment of major depressive disorders, drug plans should ensure that reimbursement is confined to patients with diabetic peripheral neuropathic pain.

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.

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