

## Duloxetine (for diabetic peripheral neuropathic pain)

### Product:

DULOXETINE (Cymbalta®)  
30mg, 60mg capsules

### Class of drugs:

Serotonin and norepinephrine reuptake inhibitor (SNRI)

### Indication:

Treatment of diabetic peripheral neuropathic pain

### Manufacturer:

Eli Lilly Canada Inc.

## CED Recommendation

The CED recommended that duloxetine (Cymbalta) be funded for the treatment of diabetic peripheral neuropathic pain through the Exceptional Access Program according to specific criteria. The CED noted that duloxetine (Cymbalta) has been shown to reduce pain and improve quality of life in the treatment of diabetic peripheral neuropathic pain. However, there is no evidence that duloxetine (Cymbalta) is as or more effective than lower cost alternatives.

## Executive Officer Decision

Based on the CED's recommendation, the Executive Officer decided to fund duloxetine (Cymbalta) through the Exceptional Access Program according to specific criteria.

## Status

Funding available through the Ontario Public Drug Programs via the Exceptional Access Program.

### Highlights of Recommendation:

- ◆ Duloxetine (Cymbalta) is indicated for the treatment of diabetic peripheral neuropathic pain (nerve pain in the arms and legs experienced by some patients with diabetes) as well as for the treatment of depression. This review is specific to its use in the management of neuropathic pain in patients with diabetes.
- ◆ The Committee evaluated three studies comparing the effects of duloxetine (Cymbalta) to placebo in adult patients with diabetic peripheral neuropathic pain. Compared with placebo, patients treated with duloxetine (Cymbalta) reported reductions in pain and improvements in their quality of life.
- ◆ There are no comparison studies between duloxetine (Cymbalta) and other treatments for diabetic peripheral neuropathic pain; therefore, its efficacy relative to alternative therapies is unknown.
- ◆ Available studies for duloxetine (Cymbalta) in the treatment of diabetic peripheral neuropathic pain were short in duration (12 weeks). The long-term safety of this drug is uncertain.
- ◆ Common side effects reported with duloxetine include nausea, dizziness, fatigue and sleepiness.
- ◆ At the recommended dose of 60mg daily, duloxetine (Cymbalta) costs \$3.56 per day. It is more expensive than alternative treatments such as amitriptyline, carbamazepine, and opioid analgesics that are listed on the Formulary. Duloxetine (Cymbalta) is similar in cost to gabapentin, a neuropathic pain treatment funded through the Exceptional Access Program.
- ◆ **Overall, the Committee acknowledged that duloxetine (Cymbalta) has been shown to reduce pain and improve quality of life in the treatment of diabetic peripheral neuropathic pain compared with placebo. However, there is no evidence that duloxetine (Cymbalta) is as or more effective than lower cost alternatives listed on the Formulary. Furthermore, the long-term safety of this drug has not been established. As such, the Committee recommended that funding be considered through the Exceptional Access Program according to specific criteria.**

### Background:

Diabetic neuropathy is a nerve disorder caused by poor blood sugar control in patients with diabetes. Diabetic peripheral neuropathy is the most common type of diabetic neuropathy. Symptoms of diabetic peripheral neuropathy include pain, numbness and tingling in the toes, feet, legs, hands, and arms.

The goal of treating diabetic peripheral neuropathy is to primarily relieve discomfort. The first step is to bring blood sugar levels under control. Drug treatments may be prescribed for the relief of pain, burning, or tingling. Analgesics, antidepressants, and anticonvulsant medications are commonly used for the management of diabetic peripheral neuropathic pain. Many of these treatments are listed on the Ontario Drug Benefit Formulary. Funding for other therapies, such as gabapentin and pregabalin, are considered through the Exceptional Access Program.

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## Detailed Discussion:

- ◆ The Committee reviewed three double-blind randomized controlled studies evaluating the efficacy and safety of duloxetine (Cymbalta) for diabetic peripheral neuropathic pain. The studies were 12 weeks in duration and compared duloxetine (Cymbalta) with placebo in a total of 1,139 patients.
- ◆ The studies reported that duloxetine (Cymbalta), at doses of 60mg daily and 60mg twice daily, was effective in reducing pain, as measured by a reduction in 24-hour average pain scores. Improvements in quality of life measures were also observed in patients who were treated with duloxetine (Cymbalta) compared with placebo.
- ◆ Duloxetine (Cymbalta) 60mg twice daily was not shown to be significantly better in pain control than the 60mg once daily dose, and the 60mg twice daily dose was associated with more adverse events.
- ◆ Because direct comparison studies between duloxetine (Cymbalta) and alternative neuropathic pain treatments are not available, its efficacy versus other agents is unknown.
- ◆ The most common side effects with duloxetine (Cymbalta) reported in the studies were sleepiness and nausea.
- ◆ There are no randomized controlled studies evaluating the long-term safety of duloxetine (Cymbalta). Given that diabetic peripheral neuropathic pain is a chronic condition, the Committee was concerned about the lack of long-term safety data. It was noted that the Food and Drug Administration in the United States recently updated warnings on the risk of hyponatremia (low blood sodium levels), bleeding, and urinary hesitancy/retention associated with the use of duloxetine (Cymbalta).
- ◆ At the recommended dose of 60mg daily, duloxetine (Cymbalta) costs \$3.56 per day. It is more expensive than alternative treatments such as amitriptyline, carbamazepine, and opioid analgesics that are listed on the Formulary. Duloxetine (Cymbalta) is similar in cost to gabapentin, which is funded through the Exceptional Access Program.
- ◆ The Committee acknowledged that diabetic peripheral neuropathic pain may sometimes be difficult to treat and that having more treatment options would be valuable in patients who do not respond to standard therapies.
- ◆ Overall, the Committee noted that duloxetine (Cymbalta) has been shown to reduce pain and improve quality of life in the treatment of diabetic peripheral neuropathic pain compared with placebo. However, there is no evidence that duloxetine (Cymbalta) is more effective than lower cost alternatives listed on the Formulary. Furthermore, the long-term safety of this drug has not been established. As such, the Committee recommended that funding be considered through the Exceptional Access Program.

## EAP Criteria:

The CED recommended that funding for duloxetine (Cymbalta) be considered through the Exceptional Access Program (EAP) according to the following clinical criteria:

- *Patients with diabetic peripheral neuropathic pain (receiving insulin and/or oral hypoglycemic agents) who have failed an adequate trial of tricyclic antidepressant and an adequate trial of gabapentin.*
- *The dose of duloxetine (Cymbalta) is limited to a maximum of 60mg daily.*

## CEDAC Recommendation:

(<http://www.cadth.ca/index.php/en/cdr/recommendations>)

The Canadian Expert Drug Advisory Committee (CEDAC) recommended that duloxetine (Cymbalta) 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 (Cymbalta) should be limited to a maximum of 60mg daily.



Ministry of  
Health and Long-Term Care  
Ontario Public Drug Programs

**For more information, please contact:**

**Ministry of Health and Long-Term Care**

Ontario Public Drug Programs

Hepburn Block, 9th Floor

80 Grosvenor Street, Queen's Park

Toronto, Ontario M7A 1R3

or click: [http://www.health.gov.on.ca/english/providers/program/drugs/ced\\_rec\\_table.html](http://www.health.gov.on.ca/english/providers/program/drugs/ced_rec_table.html)