CEDAC FINAL RECOMMENDATION

PREGABALIN RESUBMISSION
(Lyrica® – Pfizer Canada Inc.)
Indication: Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

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

Reasons for the Recommendation:

1. The Committee considered the results of three new randomized placebo-controlled trials of pregabalin in patients with diabetic peripheral neuropathy that met the CDR protocol since the original review. Two of the three trials did not show a statistically significant reduction in mean pain scores at study endpoint for pregabalin compared with placebo.
2. There are a number of drug classes used in the treatment of pain associated with diabetic peripheral neuropathy, including tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors and anticonvulsants. There are drugs in all of these classes that are less expensive than pregabalin and there is no new RCT evidence since the initial submission demonstrating that pregabalin is more effective than any of these drugs. Pregabalin and gabapentin are in the same drug class and are structural analogues of gamma-aminobutyric acid. There is no direct clinical trial evidence that pregabalin has a therapeutic advantage over gabapentin.

Background:
This resubmission for pregabalin is for the management of neuropathic pain associated with diabetic peripheral neuropathy. Pregabalin is also approved by Health Canada for the management of neuropathic pain associated with postherpetic neuralgia and pain associated with fibromyalgia. It has also been issued a Notice of Compliance with Conditions for the management of central neuropathic pain. The recommended starting dose of pregabalin in diabetic peripheral neuropathy is 150 mg daily given in two to three divided doses. The maximum approved dose is 600 mg daily given in two divided doses. Pregabalin is available in 25 mg, 50 mg, 75 mg, 150 mg, and 300 mg capsules.

Submission History:
Pregabalin was previously reviewed for the treatment of diabetic peripheral neuropathy and postherpetic neuralgia and received a CEDAC recommendation of "do not list" (see Notice of CEDAC Final Recommendation, January 25, 2006).

The original Common Drug Review (CDR) systematic review of pregabalin included six double-blind randomized controlled trials (DBRCTs) in patients with painful diabetic peripheral neuropathy (N = 1525). One of the six trials included amitriptyline 75 mg daily, which resulted in a statistically significant improvement in pain control compared with placebo whereas pregabalin did not. Higher doses of pregabalin were more likely to produce greater improvements in the pain rating scales, but they were also more likely to be associated with more frequent adverse events. The rate of discontinuation due to adverse events was 8.8% for pregabalin (all doses combined) and 3.9% for placebo. Adverse events that most frequently led to discontinuation of pregabalin include dizziness, somnolence, confusion, peripheral edema, ataxia, and asthenia. The original pharmacoeconomic model submitted by the manufacturer compared pregabalin with gabapentin and was limited by the difficulty in determining dose equivalency between these two agents.

The manufacturer's resubmission is based on a new economic model for diabetic peripheral neuropathy comparing pregabalin (150 mg to 300 mg twice daily) with duloxetine (60 mg). In addition, there were new prices for pregabalin: lower prices for 150 mg and 300 mg capsules which were included in the economic model, and higher prices for 25 mg, 50 mg and 75 mg capsules which were not considered.

Summary of CEDAC Considerations:
The Committee considered the following information prepared by the Common Drug Review: a systematic review of double-blind randomized controlled trials of pregabalin in patients with painful diabetic peripheral neuropathy and a critique of the manufacturer's pharmacoeconomic evaluation.

Clinical Trials
In addition to the six trials from the previous pregabalin CDR review, three new DBRCTs (N = 1041) were included in this systematic review:

DPN-060: Published 13-week multicentre US trial randomizing 167 patients to pregabalin 600 mg daily or placebo.
DPN-030: Unpublished 12-week multicentre international trial randomizing 412 patients to pregabalin 150 mg to 600 mg daily titrated to effect, or placebo.
DPN-071: Unpublished 13-week multicentre US trial randomizing 456 patients to pregabalin 300 mg daily, pregabalin 600 mg daily, or placebo.

The three new trials were of similar design and duration compared with the six DBRCTs included in the original review. All nine trials were placebo-controlled and one of these trials also included amitriptyline as a reference group. No trials included duloxetine, gabapentin, or other treatments used in diabetic peripheral neuropathy, as a comparator. In the three new trials, withdrawals were between 16% and 42% in the pregabalin group and were between 18% and 28% in the placebo group.

Patients who did not achieve adequate efficacy and/or could not tolerate gabapentin (doses > 1,200 mg/day), were excluded in four of the six original trials but none of the three new trials. Studies excluding gabapentin non-responders would be expected to overestimate the efficacy of pregabalin, because patients who have failed gabapentin may have a reduced response to pregabalin. Further, the generalizability of trial results to patients who are gabapentin non-responders is unknown.

In the three new trials, the proportion of patients who had received gabapentin prior to the trials was 11% to 22% but it is not known if they were gabapentin non-responders.

Outcomes

The primary outcome in the three new trials was the mean pain score at end of study. The CDR systematic review also considered the following outcomes: proportion of patients with ≥50% reduction in mean pain score, quality of life, patient global impression of change, and improvements in sleep.

Efficacy or Effectiveness

- Statistically significant differences in pain were reported for pregabalin compared with placebo in only one of the three trials (DPN-060) using between-treatment difference in mean pain score and the proportion of patients with ≥ 50% reduction in mean pain score.
- Statistically significant improvements in quality of life (measured using either the Short-Form 36 Health Survey or the European 5-Domain Quality of Life Questionnaire) and patient global impression of change scores were not consistently observed across trials and were sometimes of uncertain clinical importance. All three new trials reported improvements in sleep with pregabalin compared with placebo.

Harms (Safety and Tolerability)

- No new harms issues were identified in the three new trials. The most common adverse events reported for pregabalin were dizziness, peripheral edema, somnolence and weight increase.
- The CDR pooled analysis of nine trials found a statistically significantly higher frequency of withdrawals due to adverse events in pregabalin 300 mg and 600 mg treatment groups compared with placebo [(11% versus 5%, respectively); number needed to harm (NNH) = 17 (95% CI: 11 to 40) and 16% versus 6%; NNH = 10 (95% CI: 8 to 16)], respectively. Withdrawals due to adverse events appeared to be dose-related.

Cost and Cost-Effectiveness

At recommended doses, the daily cost of pregabalin (300 mg to 600 mg, $4.33) is higher than the daily cost of tricyclic antidepressants ($0.25 to $1.21), gabapentin (900 mg to 2400 mg, $1.46 to $3.48) and duloxetine (60 mg, $3.56). The manufacturer's cost-effectiveness and cost-utility analysis compared pregabalin 150 mg twice daily, allowing for dose increase to 300 mg twice daily where there is inadequate response, with duloxetine 60 mg daily (no dose increase permitted), in patients with painful diabetic peripheral neuropathy who have previously failed treatment with tricyclic antidepressants and gabapentin. Clinical efficacy was driven by ≥ 50% and ≥ 30% improvements in pain score from baseline. The Committee concluded that the assumptions around the clinical effects of pregabalin were not supported by the results of the

available RCTs, and therefore, there was significant uncertainty in the economic evaluation provided by the manufacturer.

Other Discussion Points:

- The Committee considered reimbursement for pregabalin as a third line agent following a trial of a tricyclic antidepressant and an anticonvulsant. There were no trials found evaluating pregabalin in this patient population and other third line options are less expensive than pregabalin. Although there are no trials evaluating duloxetine as a third-line option, duloxetine belongs to a different drug class thereby offering another therapeutic option.
- While there are no randomized controlled trials directly comparing duloxetine with pregabalin, the Committee discussed the clinical trials reviewed by CEDAC at the time of the duloxetine recommendation and noted that statistically significant reductions in pain scores were consistently observed at study endpoint in these trials.
- Limitations of the trials include the short durations of observation for a chronic condition and the high total withdrawal rates. The problem of a high placebo response in patients with painful diabetic peripheral neuropathy further limits evaluation of the data.
- No DBRCT evidence evaluating the efficacy and safety of pregabalin in combination with other treatments for painful diabetic peripheral neuropathy (e.g., tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors or opioids) was identified, despite the potential for these combinations in clinical practice.
- The Committee was aware that the Health Technology Assessment (HTA) Directorate of the Canadian Agency for Drugs and Technologies in Health (CADTH) recently released a systematic review of the efficacy and safety of anticonvulsants, serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants for treatment of neuropathic pain of any etiology. Differences in HTA and CDR reports include the types of neuropathic pain considered, the availability of unpublished literature, and the HTA report's focus on drug classes rather than individual treatments. The HTA report noted that a statistically significant difference in clinical response rates between tricyclic antidepressants, anticonvulsants and SNRIs could not be detected with appropriate statistical analyses.

CEDAC Members Participating

July 15th, 2009: Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Yvonne Shevchuk, and Dr. Kelly Zarnke.

September 16th, 2009: Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Mr. John Deven, Dr. Michael Evans, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Yvonne Shevchuk, and Dr. Kelly Zarnke.

Regrets

July 15th, 2009: Dr. Michael Evans.

September 16th, 2009: None.

Conflicts of Interest
One CEDAC member reported receiving institutional funding through Pfizer Canada Inc. but no direct payments were received and funding was not related to pregabalin, therefore, this did not preclude participation in the discussion and voting.

About this Document:
CEDAC provides formulary listing recommendations to publicly funded drug plans.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation. An overview of these reviews, as well as a plain language version of this document is posted on the CADTH website when available.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the CDR Confidentiality Guidelines.

The CEDAC Final Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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