

CEDAC FINAL RECOMMENDATION

LACOSAMIDE

(Vimpat – UCB Canada Inc.)

Indication: Epilepsy, Partial-Onset Seizures

Recommendation:

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that lacosamide be listed as adjunctive therapy in patients with refractory partial-onset seizures who meet all of the following criteria:

- are under the care of a physician experienced in the treatment of epilepsy, and
- are currently receiving two or more antiepileptic drugs, and
- in whom all other antiepileptic drugs are ineffective or not appropriate.

Reasons for the Recommendation:

1. In three double-blind randomized controlled trials (RCTs), included in the systematic review considered by CEDAC, lacosamide achieved statistically significant reductions in seizure frequency compared with placebo.
2. Lacosamide is more costly compared with other antiepileptic drugs.

Of Note:

The Committee noted the numerically higher frequency of serious adverse events, cardiac events, and hospitalizations in lacosamide-treated patients compared with placebo.

Background:

Lacosamide has a Health Canada indication as adjunctive therapy in the management of partial-onset seizures in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy. Lacosamide is a functionalized amino acid molecule believed to exert its anticonvulsant effect through enhancement of slow inactivation of voltage-gated sodium channels. It is available as oral tablets (50 mg, 100 mg, 150 mg, and 200 mg) and as an intravenous (IV) solution (10 mg/mL), although the manufacturer is not seeking reimbursement for the IV solution at this time.

The recommended starting dose is 50 mg twice daily, which should be increased to an initial therapeutic dose of 100 mg twice a day after one week. Depending on patient response and

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tolerability, the maintenance dose can be further increased by 50 mg twice a day every week, to a maximum recommended daily dose of 400 mg (200 mg twice a day).

Summary of CEDAC Considerations:

The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of three double-blind RCTs of lacosamide, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Clinical Trials

The systematic review included three double-blind RCTs of adjunctive treatment of partial-onset seizures in adults:

- Study SP667 (N = 497) was a multinational study that included four treatment groups: placebo, lacosamide 200 mg, lacosamide 400 mg, and lacosamide 600 mg.
- Study SP755 (N = 546) was a multinational study that included three treatment groups: placebo, lacosamide 200 mg, and lacosamide 400 mg.
- Study SP754 (N = 489) was a multi-centre study conducted exclusively in the United States and included three treatment groups: placebo, lacosamide 400 mg, and lacosamide 600 mg.

Patients enrolled in the above trials were required to have a two-year history of partial-onset seizures despite treatment with two or more antiepileptic drugs, and to be on a stable dose of one or two (SP667) or one to three (SP754, SP755) antiepileptic drugs, with or without vagus nerve stimulation, all of which were to be maintained at pre-trial doses for the duration of the trial.

All three trials had an eight-week baseline phase, followed by a titration phase (four or six weeks) and a maintenance phase (12 weeks). Total trial duration was 26 weeks in SP667 and SP754, and 24 weeks in SP755.

Median 28-day baseline seizure frequencies ranged from 11 to 13, 9.9 to 10.3, and 11.5 to 15 across treatment groups in studies SP667, SP755, and SP754, respectively (excluding the lacosamide 600 mg treatment groups). A considerable proportion of patients in all three trials had undergone prior surgery for epilepsy, ranging from approximately 20% in study SP755 to more than 50% in study SP754. The percentages of patients discontinuing from the studies were 25% (study SP667), 18% (study SP755), and 22% (study SP754). In all three trials, higher proportions of patients withdrew from the lacosamide groups compared with the placebo group.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: seizure frequency, percentage of patients achieving seizure-free status, quality of life, serious adverse events, withdrawal due to adverse events, and hospitalizations.

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The co-primary outcomes in all three trials were the same: the change in seizure frequency per 28-day period from baseline to maintenance period, and the proportion of patients with a 50% or greater reduction in seizure frequency per 28 days from baseline to maintenance period. An outcome noted to be of importance to patients and caregivers was caregiver time, which was measured in two trials.

Results

The majority of patients (> 80%) were receiving two or more antiepileptic drugs as background therapy in all three trials. Results presented below focus on lacosamide daily doses of 200 mg or 400 mg, as a daily dose of 600 mg exceeds the dose recommended by Health Canada.

Efficacy or Effectiveness

- Reductions in 28-day seizure frequency from baseline to maintenance phase were statistically significantly greater for lacosamide 400 mg compared with placebo in all three trials, and statistically significantly greater for lacosamide 200 mg compared with placebo in SP755. However, median reductions from baseline in 28-day seizure frequency were numerically small; median reductions in the lacosamide 400 mg treatment groups were –3, –3.4, and –3.9 in SP667, SP755, and SP754, respectively, versus –1, –2.6, and –2.9 in the respective placebo groups.
- In all trials, a 50% or greater reduction in seizure frequency compared with baseline was achieved by a statistically significantly higher proportion of patients treated with lacosamide 400 mg compared with placebo: 41% versus 22% (SP667), 41% versus 26% (SP755), and 38% versus 18% (SP754). However, the trial reports did not provide sufficient detail to determine whether observed reductions occurred mainly in mild or more severe seizures. The proportion of patients achieving a 50% or greater reduction in seizure frequency did not differ statistically between lacosamide 200 mg and placebo in either SP667 or SP755.
- The percentage of patients achieving seizure-free status was 6% or less across all treatment groups across all trials; the statistical significance of between-treatment differences was not reported.
- There were no apparent differences between lacosamide and placebo in terms of quality of life scores or caregiver time spent.

Harms (Safety and Tolerability)

- The proportions of patients experiencing serious adverse events and hospitalization were numerically higher in the lacosamide-treated patients compared with placebo. Across the trials, withdrawal due to adverse events ranged from 15% to 19% in the lacosamide 400 mg groups, compared with 5% in the placebo groups.
- The proportion of patients experiencing an increase in seizure frequency of 25% or greater was similar for all treatments based on pooled data from all trials: lacosamide 200 mg (15%), lacosamide 400 mg (16%), and placebo (18%).

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing lacosamide plus standard therapy with standard therapy alone in patients with partial-onset seizures (with or without generalization) who failed one to three concomitant antiepileptic drugs. Clinical efficacy was based on the proportion of patients achieving a 50% reduction in seizure frequency, obtained

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from the three placebo-controlled trials included in the systematic review. It was assumed that all patients achieving this outcome would have a 75% reduction in seizures, while patients with less than a 50% reduction in seizure frequency were assumed to have no change in seizure frequency from baseline, and lacosamide would be withdrawn. Utility scores were obtained from a published study conducted in 1997, in 81 Italian patients with poorly controlled seizures who were initiated on adjunctive treatment with lamotrigine.

The manufacturer reported a cost per quality-adjusted life-year (QALY) estimate of \$39,156 for lacosamide plus standard therapy compared with standard therapy alone over a two-year analysis period, with estimates ranging from \$35,921 to \$67,706 in sensitivity analyses. CDR noted an alternative published source for utility scores, which, when applied to the manufacturer's model, generated a cost per QALY estimate of \$86,000.

The daily cost of lacosamide is \$6.64 to \$10.64 (200 mg to 400 mg daily); other commonly used antiepileptic drugs and their costs include carbamazepine (\$0.32 to \$0.48), lamotrigine (\$1.10 to \$1.49), topiramate (\$1.19 to \$1.77), phenytoin (\$0.39 to \$0.52), and levetiracetam (\$2.35 to \$6.40).

Patient Input Information:

The following is a summary of information provided by nine patient groups who responded to the CDR Call for Patient Input:

- Information submitted by patient groups emphasized the significant negative impact of epilepsy on quality of life. Reduced quality of life for patients with epilepsy is related to limitations on daily activities (e.g., driving, employment choices), as well as psychosocial distress due to stigmatization and worry related to having seizures in public and possible loss of bladder and/or bowel control. For caregivers, uncontrolled epilepsy was noted to result in stress and a substantial impact on caregiver time.
- Patient groups also indicated that current medications do not provide adequate seizure control for all patients. In addition, adverse events experienced with current medications were noted (sedation, weight gain, psychological changes, reduced libido, and Stevens–Johnson Syndrome).
- Patient expectations for lacosamide include decreased incidence of seizures and fewer adverse events compared with current medications.

Other Discussion Points:

- The Committee considered that despite the availability of numerous antiepileptic drugs, there remains an unmet need in a condition with substantial impact on quality of life.
- Clinical experience with lacosamide is less than that of other antiepileptic drugs, and the periodic safety update reports for lacosamide identified a number of important safety concerns, including neurological and cardiac adverse events.

CEDAC Members Participating:

Dr. Robert Peterson (Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, and Dr. Yvonne Shevchuk.

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Regrets:

Dr. Anne Holbrook (Vice-Chair)

Conflicts of Interest:

None

About this Document:

CEDAC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CEDAC deliberations.

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

The Final CEDAC 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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