Canadian Expert Drug Advisory Committee
Final Recommendation – Plain Language Version

LACOSAMIDE
(Vimpat – UCB Canada Inc.)
Indication: Epilepsy, Partial-Onset Seizures

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that Vimpat, which is also called lacosamide, be listed by Canada's publicly funded drug plans as adjunctive (add-on) therapy in patients with refractory (unmanageable) 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 not working or cannot be used.

Reasons for the Recommendation:

1. In three studies reviewed by CEDAC, Vimpat decreased the frequency of seizures compared with placebo (a tablet containing no active medication).
2. Vimpat is more costly compared with other antiepileptic drugs.

Of Note:
The Committee noted that a higher percentage of Vimpat-treated patients had serious side effects, heart problems, and hospitalizations compared with those who received placebo.

Background:
Vimpat belongs to a class of drugs called antiepileptics. It works in the brain to block the spread of seizure activity. The precise way that Vimpat works to treat partial-onset seizures is unknown. Vimpat is approved by Health Canada as adjunctive therapy in the management of partial-onset seizures in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy.

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 a dose of 100 mg twice a day after one week. Depending on patient response and side effects, this 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:
To make their decision, the Committee considered the following information prepared by the Common Drug Review (CDR): a review of the medical studies of Vimpat and a review of economic information prepared by the manufacturer of Vimpat. Also, CEDAC considered information that patient groups submitted about outcomes and issues important to patients who have the condition for which the drug is indicated or who might use the drug.

Clinical Trials
The review included three studies using Vimpat as adjunctive treatment of partial-onset seizures in adults:

- Study SP667, with 497 patients, was a multinational (more than one country) study that included four treatment groups: placebo, Vimpat 200 mg, Vimpat 400 mg, and Vimpat 600 mg.
- Study SP755, with 546 patients, was a multinational study that included three treatment groups: placebo, Vimpat 200 mg, and Vimpat 400 mg.
- Study SP754, with 489 patients, was a study that took place in more than one clinic in the United States and included three treatment groups: placebo, Vimpat 400 mg, and Vimpat 600 mg.

Patients who were included in the studies had to have had partial-onset seizures despite treatment with two or more antiepileptic drugs for at least two years. They also had to be on a constant dose of one or two (SP667) or one to three (SP754, SP755) antiepileptic drugs, with or without vagus nerve stimulation (a procedure used to treat some forms of epilepsy), all of which were to be continued at the same doses during the study.

All three studies included three different phases. Studies began with an eight-week “observation phase,” which was followed by a “titration phase” (four or six weeks), which involved starting Vimpat or placebo and adjusting the dose. Finally, all studies had a “maintenance phase” (12 weeks), during which the dose of the study medication was kept constant. Total length of the study was 26 weeks in SP667 and SP754, and 24 weeks in SP755.

The average number of seizures over 28 days during the observation phase 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 Vimpat 600 mg treatment groups). Many patients in all three studies had previously had surgery for epilepsy, ranging from approximately 20% in study SP755 to more than 50% in study SP754. The percentages of patients discontinuing the studies were 25% (study SP667), 18% (study SP755), and 22% (study SP754). In all three studies, the percentage of patients that stopped participating in the study was higher in the Vimpat groups compared with placebo groups.

Outcomes

Outcomes were defined in advance in the CDR systematic review protocol. Of these, the Committee discussed the following: seizure frequency, percentage of patients who became free of seizures, quality of life, serious side effects, stopping participation because of side effects, and hospitalizations.

The main purpose of all three studies was the same, to measure both: the change in the 28-day seizure frequency (change in the number of seizures over a 28-day period) from the observation phase to the maintenance phase, and the proportion of patients with a 50% or greater reduction in the 28-day seizure frequency from the observation phase to the maintenance phase.

An outcome noted to be of importance to patients and caregivers was caregiver time, which was measured in two studies.

Results

The majority of patients (more than 80%) were receiving two or more antiepileptic drugs, in addition to the study treatment, in all three studies. The results shown below focus on Vimpat daily doses of 200 mg or 400 mg, as a daily dose of 600 mg is higher than what is recommended by Health Canada.

Efficacy or Effectiveness

- In all three studies, Vimpat 400 mg showed a greater decrease in the 28-day seizure frequency from the observation phase to the maintenance phase, compared with placebo. However, average decreases in 28-day seizure frequency were small; average decreases in the Vimpat 400 mg treatment groups were –3, –3.4, and –3.9 in SP667, SP755, and SP754 respectively, compared with –1, –2.6, and –2.9 in the respective placebo groups. Vimpat 200 mg showed a greater decrease in the 28-day seizure frequency from the observation phase to the maintenance phase, compared with placebo, in study SP755 only.
- In all studies, a higher percentage of patients on Vimpat 400 mg compared with placebo had a 50% or greater decrease in the 28-day seizure frequency from the observation phase to the maintenance phase: 41% versus 22% (SP667), 41% versus 26% (SP755), and 38% versus 18% (SP754). However, the study reports did not provide enough detail on whether these decreases occurred mainly in mild or more severe seizures. The percentage of patients achieving a 50% or greater reduction in the 28-day seizure frequency was about the same for Vimpat 200 mg and placebo in both SP667 and SP755.
- The percentage of patients who became free of seizures was 6% or less in all treatment groups in all studies.
- There were no obvious differences between Vimpat and placebo in terms of quality of life scores or caregiver time spent.

Harms (Safety and Tolerability)

- The percentage of patients experiencing serious side effects and hospitalization was numerically higher for patients receiving Vimpat compared with placebo. Across the studies, the percentage of patients stopping participation because of side effects ranged from 15% to 19% in the Vimpat 400 mg groups compared with 5% in the placebo groups.
- The percentage of patients who had an increase in seizure frequency of 25% or greater was similar for all treatments based on combined data from all studies: Vimpat 200 mg (15%), Vimpat 400 mg (16%), and placebo (18%).

Cost and Cost-Effectiveness

The manufacturer submitted economic information to compare Vimpat plus standard therapy with standard therapy alone in patients with partial-onset seizures, to evaluate the health benefit. Patients in this evaluation had not improved enough when taking from one to three antiepileptic drugs. The effectiveness of Vimpat was based on the percentage of patients achieving at least a 50% decrease in seizure frequency in the three studies reviewed by CEDAC. The manufacturer assumed that the group of patients that achieved at least a 50% decrease in seizure frequency would have had a 75% decrease in seizure frequency. The manufacturer also assumed that patients who had less than a 50% decrease in seizure frequency would have had no change in seizure frequency, and therefore would have had their Vimpat stopped. Other data were obtained from a published study conducted in 1997, in 81 Italian patients with poorly controlled seizures who were started on additional treatment with lamotrigine (another antiepileptic drug, which is also called Lamictal).

The daily cost of Vimpat is $6.64 to $10.64 (200 mg to 400 mg daily); other commonly used antiepileptic drugs and their daily costs include carbamazepine (also called Tegretol, $0.32 to $0.48), lamotrigine (Lamictal, $1.10 to $1.49), topiramate (Topamax, $1.19 to $1.77), phenytoin (Dilantin, $0.39 to $0.52), and levetiracetam (Keppra, $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:

- Patient groups stressed the very bad effect that epilepsy has on quality of life. Decreased quality of life for patients with epilepsy results from limitations on daily activities (e.g., driving, employment choices) as well as stress due to being identified as an epileptic and worry about having seizures in public and possible loss of bladder and/or bowel control. For caregivers, uncontrolled epilepsy was noted to result in stress and increased demand for caregivers' time.
- Patient groups also mentioned that current medications do not provide enough seizure control for all patients. In addition, they noted side effects of currently available medications, such as sleepiness, weight gain, psychological changes, decreased sex drive, and Stevens–Johnson Syndrome (a skin problem that can be serious).
- Patients expect that Vimpat treatment will result in less frequent seizures and fewer side effects compared with current medications.

Other Discussion Points:

- The Committee felt that although many antiepileptic drugs are available, there is still an unmet need in this condition that affects quality of life.
- Vimpat has been used for a shorter period of time compared with other antiepileptic drugs and the periodic safety update reports for Vimpat identified a number of important safety concerns, including nerve and heart side effects.

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.

Regrets:
Dr. Anne Holbrook (Vice-Chair)

Conflicts of Interest:
None

About this Document
The information contained within this plain language version of the Canadian Expert Drug Advisory Committee (CEDAC) Recommendation about this drug is based on the information found within the corresponding technical version of the CEDAC Recommendation.

In making its recommendation, CEDAC considered the best clinical and pharmacoeconomic evidence available, up to that time. Health care professionals and those requiring more detailed information are advised to refer to the technical version available in the CDR Drug Database on the CADTH website (www.cadth.ca).

Background on CEDAC
CEDAC is a committee of the Canadian Agency for Drugs and Technologies in Health (CADTH). The Committee is made up of drug evaluation experts and public members. CEDAC provides recommendations about whether or not drugs should be listed for coverage through the participating publicly funded drug plans; however, the individual drug plans make their own decision about whether or not to cover a drug.

In making its recommendations, CEDAC decides if the drug under review ought to be covered by the participating public drug plans based on an evidence-informed review of the medication's effectiveness and safety, and based on an assessment of its cost-effectiveness in comparison with other available treatments. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CEDAC deliberations.

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The manufacturer has reviewed this document and has not requested the deletion of any confidential information.