CDEC FINAL RECOMMENDATION

PERAMPANEL
(Fycompa — Eisai Limited)
Indication: Epilepsy, Partial-Onset Seizures

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that perampanel be listed as an adjunctive therapy in the management of partial-onset seizures in patients with epilepsy who are not satisfactorily controlled with conventional therapy, if the following clinical criteria and condition are met:

Clinical Criteria:
- Patients are currently receiving two or more antiepileptic drugs (AEDs).
- Less costly AEDs are ineffective or not appropriate.

Condition:
- Patients are under the care of a physician experienced in the treatment of epilepsy.

Reasons for the Recommendation:
1. Three randomized controlled trials (RCTs) demonstrated that treatment with perampanel resulted in statistically significant and clinically meaningful reductions in seizure frequency per 28 days compared with placebo.

2. At the submitted price of [redacted], perampanel is less costly than lacosamide for adjunctive therapy in the management of partial-onset seizures in adult patients with epilepsy.

Of Note:
CDEC noted that the use of perampanel in combination with lacosamide has not been studied and that the combination of perampanel and lacosamide would be more costly than other combinations of AEDs.

Background:
Perampanel is an AED, indicated as adjunctive therapy in the management of partial-onset seizures in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy. In the absence of enzyme-inducing AEDs, the product monograph recommends a starting dose of 2 mg per day. The dose may be increased, based on clinical response and tolerability, by increments of 2 mg up to 8 mg per day. Dose increases should occur no more

© 2013 CADTH

frequently than at two-week intervals. In the presence of enzyme-inducing AEDs, the recommended starting dose is 4 mg per day. Based on clinical response and tolerability, the dose may be increased by increments of 2 mg to a maximum dose of 12 mg per day. Dose increases should occur no more frequently than at one-week intervals.

Perampanel is available as 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg tablets.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs for perampanel, a critique of the manufacturer's pharmacoeconomic evaluation, and patient-group submitted information about outcomes and issues important to patients.

Patient Input Information
The following is a summary of information that was provided by three patient groups that responded to the CDR call for patient input:

- A reduction in the absolute number of seizures, even without full control, can potentially improve quality of life by increasing the individual's freedom to seek out employment or otherwise participate in life, while reducing the number of emergency calls, ambulance rides, hospital stays, physician visits, and diagnostic investigations.
- The families of people whose seizures are not controlled also live with epilepsy. Caregivers worry about being over-protective, often suffer from insomnia, sometimes burn out, and frequently see their own incomes and career prospects diminished.
- People living with epilepsy noted that currently available medications for epilepsy have adverse effects, some of which may be intolerable to the individual, including inability to concentrate, memory problems, turbulent mood swings, fatigue, kidney and liver failure, sexual dysfunction, depression, and suicidal ideation.
- The groups hope that perampanel will improve the lives of some who currently suffer from uncontrolled or partially controlled seizures.

Clinical Trials
Three multicentre, double-blind, parallel-group, randomized, placebo-controlled, phase III superiority trials met the inclusion criteria for the CDR systematic review. Study 304 (N = 390), Study 305 (N = 389), and Study 306 (N = 712), were identical in design, with the exception of the perampanel doses. All trials enrolled patients 12 years and older with uncontrolled partial-onset seizures, with or without secondarily generalized seizures, despite receiving one to three AEDs. In Studies 304 and 305, patients were randomized to perampanel 8 mg once daily, perampanel 12 mg once daily, or placebo. In Study 306, patients were randomized to perampanel 2 mg once daily, perampanel 4 mg once daily, perampanel 8 mg once daily, or placebo. The duration of double-blind treatment in all studies was 19 weeks (i.e., a 6-week titration phase and a 13-week maintenance phase).

Outcomes
Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Per cent change in the frequency of all partial seizures per 28 days.
- Responder rate — defined as the percentage of patients who experienced a 50% or greater reduction from baseline in seizure frequency per 28 days during double-blind treatment.

© 2013 CADTH

- Seizure-free status — defined as the proportion of patients with 100% seizure reduction.
- Quality of life — measured using the Quality of Life in Epilepsy (QOLIE)-31-P, a self-reported questionnaire comprised of 31 items that are assessed on a four to six-point Likert scale.
- Patient or Clinician's Global Impression of Change — measured using a questionnaire that assesses the patient's clinical status during the preceding four weeks and evaluates seizure frequency, seizure severity/intensity, adverse events, and overall functional status using a seven-point scale.

The primary efficacy outcome for all studies was the change in seizure frequency per 28 days relative to baseline during the double-blind treatment phase.

Results

Efficacy

- There were statistically significantly greater median per cent reductions in seizure frequency per 28 days with perampanel (all doses) compared with placebo in all three studies, with the exception of the 2 mg group in Study 306. The median difference (95% confidence interval [CI]) in per cent change in seizure frequency was reported as follows:
  - Perampanel 4 mg versus placebo: –13.7% (–23.3% to –4.5%) in Study 306.
  - Perampanel 8 mg versus placebo: –13.5%(–26.2% to –1.9%) in Study 304; –19.1% (–29.2% to –8.4%) in Study 305; and –20.1% (–29.7% to –10.4%) in Study 306.
  - Perampanel 12 mg versus placebo: –14.2% (–25.0% to –2.7%) in Study 304; and –13.7% (–25.2% to –2.3%) in Study 305.
- CDR's calculated relative risk (95% CI) for demonstrating at least a 50% reduction in seizure frequency per 28 days from baseline was:
  - Perampanel 4 mg versus placebo: 1.6% (1.05% to 2.52%) in Study 306.
  - Perampanel 8 mg versus placebo: 1.5% (1.03% to 2.27%) in Study 304; 2.2% (1.30% to 3.60%) in Study 305; and 2.2% (1.44% to 3.29%) in Study 306.
  - Perampanel 12 mg versus placebo: 1.3% (0.86% to 1.97%) in Study 304; and 2.4% (1.43% to 3.93%) in Study 305.
- For Patient's Global Impression of Change, a statistically significant difference between perampanel and placebo for the combined categories of "very much improved" and "improved" was demonstrated only for perampanel 8 mg in Study 305 ($P = 0.0207$).
- For Clinician's Global Impression of Change, statistically significant differences for the combined categories of "very much improved" and "improved" were demonstrated for perampanel 8 mg in all three studies ($P < 0.01$) and perampanel 4 mg in Study 306 ($P = 0.0063$).
- No statistical analyses were conducted to compare differences in QOLIE-31-P scores between treatment groups.

Harms (Safety and Tolerability)

- The proportion of patients who experienced at least one adverse event was similar between placebo (54.6% to 82.6%) and perampanel (61.7% to 91.8%). The most common adverse events associated with perampanel treatment were central nervous system-related, most frequently dizziness, somnolence, and headache.

© 2013 CADTH

- The proportion of patients with at least one serious adverse event was similar between perampanel and placebo-treated patients in all three studies (ranging from 3.3% to 9.9% with perampanel and 4.9% to 5.0% with placebo).
- Across the three trials, withdrawals due to adverse events ranged from 6.7% to 19.4% in perampanel-treated patients and 3.8% to 6.6% of placebo-treated patients. Withdrawals due to adverse events with perampanel appeared to increase in a dose-dependent manner, with the highest frequency occurring in the perampanel 12 mg groups (19.4% in Study 304 and 19.0% in Study 305).

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis, where only drug costs were considered, comparing perampanel with lacosamide. Similar clinical efficacy and safety between perampanel and lacosamide were assumed by the manufacturer based on the results of an indirect comparison. The submitted price for perampanel is [redacted] per tablet, or [redacted] per day. Based on recommended doses, the annual drug costs for perampanel ([redacted]; 4 mg to 12 mg per day) is lower than lacosamide ($2,453 to $3,905; 200 mg to 400 mg per day). However, the annual cost of perampanel is greater than lamotrigine ($137 to $675; 100 mg to 500 mg per day) and topiramate ($433 to $646; 200 mg to 400 mg per day). Depending on the dosages, perampanel can be less costly, more costly, or similar in cost to levetiracetam ($996 to $2,836; 1,000 mg to 3,000 mg per day).

Other Discussion Points:

CDEC noted the following:

- A CDR analysis of the cost implications of concomitant use of lacosamide and perampanel suggested that the potential cost savings attributable to perampanel would be eliminated if patients use perampanel and lacosamide concomitantly. In this case, the combination of perampanel and lacosamide would be more costly than other combinations of AEDs.
- The manufacturer submitted a cost-minimization analysis; however, CDEC felt that a cost-effectiveness analysis, which fully explores potential differences in clinical outcomes between perampanel and comparators, would have facilitated a better understanding of the cost-effectiveness of different therapies.
- The manufacturer's network meta-analysis, the basis for the suggested similar efficacy for perampanel and lacosamide, is associated with uncertainty due to a high degree of imprecision in the indirect effect estimates.
- The perampanel product monograph contains a warning regarding the risk of serious or life-threatening psychiatric and behavioural adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats in patients taking the drug.

Research Gaps:

CDEC noted that there is an absence of evidence regarding the following:

- Direct comparisons of perampanel against other AEDs such as lacosamide.
- Data regarding the long-term safety and efficacy of perampanel.
- Data regarding the maximal effective dosing for patients on concomitant CYP3A enzyme-inducing AEDs.

© 2013 CADTH

CDEC Members:

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani

September 18, 2013 Meeting

Regrets:

One CDEC member could not attend the meeting.

Conflicts of Interest:

None

About This Document:

CDEC provides formulary listing recommendations or advice to CDR participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

CADTH is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial, territorial, or federal government or the manufacturer.

© 2013 CADTH