CDEC FINAL RECOMMENDATION

ESLICARBAZEPINE ACETATE
(Aptiom — Sunovion Pharmaceuticals Canada Inc.)
Indication: Partial-Onset Seizures in Patients With Epilepsy

This document was originally issued on April 16, 2015 and was revised on June 24, 2015. References to patient perspectives regarding surgery and vagal nerve stimulation were removed from the second bullet under the heading "Patient Input Information" (page 2) as they were erroneously perceived by stakeholders as being reflective of the Canadian Drug Expert Committee's (CDEC) opinion.

Recommendation:
CDEC recommends that eslicarbazepine acetate be listed as an adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy who are not satisfactorily controlled with conventional therapy, if the following clinical criteria and conditions are met:

Clinical criteria:
- Currently receiving two or more antiepileptic drugs (AEDs)
- For whom less costly AEDs are ineffective or not clinically appropriate.

Conditions:
- Under the care of a physician experienced in the treatment of epilepsy
- The daily cost of treatment with eslicarbazepine acetate should not exceed the daily cost of alternative adjunctive therapies.

Reasons for the Recommendation:
- In four double-blind, parallel-group, placebo-controlled, phase 3 randomized controlled trials (RCTs), seizure frequency was statistically significantly reduced in patients taking eslicarbazepine acetate compared with placebo, and a greater proportion of patients taking eslicarbazepine acetate achieved a 50% reduction in seizures compared with placebo.
- At the submitted price ($[redacted] per 200 mg, 400 mg, 600 mg, or 800 mg tablet), treatment with eslicarbazepine acetate has a lower daily cost than treatment with some other adjunctive AEDs, including lacosamide ($7.06 per day) and perampanel ($9.45 per day).
- For patients who require a 1,200 mg daily dose of eslicarbazepine acetate, the daily cost of two 600 mg tablets would be greater than the cost of one and a half 800 mg tablets.

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

Background:
Eslicarbazepine acetate is indicated as adjunctive therapy in the management of partial-onset seizures in adult patients who are not satisfactorily controlled with conventional therapy. The product monograph recommends a starting dose of 400 mg once daily, which should be increased to the recommended maintenance dose of 800 mg once daily after one or two weeks. For some patients, therapy may be initiated at 800 mg once daily if the need for seizure control outweighs a potentially increased risk of adverse events during initiation. Based on individual response and tolerability, the dose may be increased to a maximum of 1,200 mg once daily. Eslicarbazepine acetate is available as 200 mg, 400 mg, 600 mg, and 800 mg tablets.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs and pivotal studies, a critique of the manufacturer's pharmacoeconomic evaluation, and a summary of information submitted by patient groups about outcomes and issues important to individuals living with partial-onset seizures.

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

- Partial-onset seizures can affect almost every aspect of a person's day-to-day life, including loss of independence, the ability to seek or maintain employment, and the ability to operate a motor vehicle safely and maintain a driver's licence. Not knowing when a seizure might occur can result in persistent anxiety or other mood disorders. Societal attitudes have a significant impact on persons with epilepsy; people with the condition often face stigma, discrimination, and social isolation.
- Current drug therapies are limited by adverse effects, including cognitive and behavioural disturbances, excessive hair growth, sexual difficulties, gum overgrowth, thinning of bones, fatigue, mood swings, and depression.
- Patient groups noted that they would like new therapies to stop or reduce the number of partial-onset seizures and to cause less cognitive dysfunction than other epilepsy medications. Most patients indicated that even a moderate reduction in the frequency of their seizures would make a major difference in their lives, although a few said they would still be very anxious.

Clinical Trials
The CDR systematic review included four multi-centre, double-blind, parallel-group, placebo-controlled, phase 3 RCTs. Study 301 (N = 402), Study 302 (N = 395), Study 303 (N = 253), and Study 304 (N = 653) enrolled patients with uncontrolled partial-onset seizures with or without secondary generalized seizures, despite receiving AEDs. Patients with seizure types other than partial-onset seizures (e.g., generalized seizures), status epilepticus, or cluster seizures within three months prior to screening were excluded. Patients were randomized to eslicarbazepine acetate 400 mg once daily (studies 301 and 302 only), eslicarbazepine acetate 800 mg once

daily, eslicarbazepine acetate 1,200 mg once daily, or placebo. The duration of the double-blind treatment in all studies was 16 weeks (4 weeks of titration and 12 weeks of maintenance). Based on the recommended dosing for eslicarbazepine acetate, CDEC focused its discussion on the results reported for the 800 mg and 1,200 mg dosing regimens.

Outcomes

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

- Seizures measured as:
  - Seizure frequency over the 12-week maintenance period (standardized to frequency per four weeks), which was the primary outcome in all four trials
  - Proportion of seizure-free patients (100% seizure reduction)
  - Proportion of patients with a 50% or greater reduction in seizure frequency
  - Proportion of patients with a 25% or greater increase in seizure frequency.
- Patient-reported outcomes:
  - Quality of Life in Epilepsy 31 items (QOLIE-31) — a measure of emotional well-being, social functioning, energy and fatigue, cognitive functioning, seizure worry, medication effects, and overall quality of life in the previous 28 days
  - Seizure Severity Questionnaire (SSQ) — a measure of seizure severity as a treatment response by characterizing changes in disruption attributed to seizures and the severity of specific seizure characteristics.
- Clinical Global Impression (CGI) — consists of three components: Severity of Illness (CGI-S), Global Improvement (CGI-I), and the Efficacy Index (CGI-E).

Efficacy

- Seizure frequency per four weeks was statistically significantly lower in the eslicarbazepine acetate groups compared with placebo, with the exception of one comparison in Study 304 that was not statistically significant. The least squares mean differences versus placebo were reported as:
  - Study 301: –1.9 (P = 0.0028) for 800 mg and –2.2 (P = 0.0003) for 1,200 mg
  - Study 302: –2.7 (P = 0.002) for 800 mg and –2.8 (P = 0.001) for 1,200 mg
  - Study 303: –1.6 (P = 0.048) for 800 mg and –1.9 (P = 0.021) for 1,200 mg
  - Study 304: –1.4 (P = 0.058) for 800 mg and –1.9 (P = 0.004) for 1,200 mg.
- There was generally no statistically significant difference between eslicarbazepine acetate and placebo for the proportion of patients who achieved seizure-free status over the maintenance phase of the trials, with the exception of eslicarbazepine acetate 1,200 mg versus placebo in Study 302 (P = 0.042).
- A statistically significantly greater proportion of eslicarbazepine acetate-treated patients achieved a 50% reduction in seizures compared with placebo-treated patients during the maintenance phase, with the exception of eslicarbazepine acetate 800 mg compared with placebo in Study 303 and Study 304. The relative risk calculated by CDR of achieving a 50% reduction in seizure frequency was (eslicarbazepine acetate versus placebo):
  - Study 301: 1.7 (95% confidence interval [CI], 1.1 to 2.8) for 800 mg and 2.2 (95% CI, 1.4 to 3.4) for 1,200 mg
  - Study 302: 1.8 (95% CI, 1.1 to 3.0) for 800 mg and 1.9 (95% CI, 1.2 to 3.2) for 1,200 mg
  - Study 303: 1.5 (95% CI, 0.9 to 2.5) for 800 mg and 1.7 (95% CI, 1.0 to 2.7) for 1,200 mg
  - Study 304: 1.3 (95% CI, 1.0 to 1.8) for 800 mg and 1.8 (95% CI, 1.4 to 2.5) for 1,200 mg.

- There were no statistically significant differences between eslicarbazepine acetate and placebo in QOLIE-31 overall score, SSQ overall score, and CGI global improvement score.

Harms (Safety and Tolerability)

- The proportion of patients with at least one serious adverse event ranged from 4% to 7% with eslicarbazepine acetate 800 mg and from 1% to 6% with eslicarbazepine acetate 1,200 mg, compared with 0% to 4% for placebo groups. The types of serious adverse events included vertigo, hyponatremia, vomiting, exanthem, and dizziness. There were two deaths in the placebo groups; one patient died due to hypothermia and another died of respiratory failure. One patient randomized to the eslicarbazepine acetate 800 mg group died of status epilepticus while taking eslicarbazepine acetate 400 mg in the titration phase.
- The proportion of patients withdrawing due to adverse events ranged from 8% to 19% with eslicarbazepine acetate 800 mg, 11% to 26% with eslicarbazepine acetate 1,200 mg, and 3% to 8% with placebo across trials. The reasons for stopping eslicarbazepine acetate treatment included dizziness, nausea, and vomiting.
- The proportion of patients who experienced at least one treatment-emergent adverse event ranged from 50% to 67% in the eslicarbazepine acetate 800 mg groups and 61% to 78% in the eslicarbazepine acetate 1,200 mg groups. Dizziness was the most commonly reported adverse event associated with eslicarbazepine acetate, occurring in 14% to 44% of patients, compared with fewer than 10% of patients given placebo. Dizziness was more commonly reported in patients receiving 1,200 mg per day compared with those receiving 800 mg per day. Other common adverse events in the active groups included headache, somnolence, diplopia, nausea, and vomiting.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing the drug costs of eslicarbazepine acetate to lacosamide and perampanel when used as adjunctive therapy to concomitant AEDs for the treatment of adults with refractory partial-onset seizures who are not adequately controlled on conventional therapy. Inadequate control was defined as epileptic seizures that are not controlled on a stable dose of at least one AED to reflect the population of the eslicarbazepine acetate pivotal trials. The perspective was that of a Canadian public drug plan with a time horizon of a single day of therapy. The assumption of clinical similarity among the three agents was based on the results of a manufacturer-funded, unpublished network meta-analysis (NMA). Costs for lacosamide and perampanel were derived using Ontario Drug Benefit formulary list prices and dose-weighted using IMS PharmaStat Ontario public data. Costs for eslicarbazepine acetate were derived using the manufacturer's submitted price of $[redacted] per tablet (200 mg, 400 mg, 600 mg, 800 mg) and by assuming that 20.7% of patients would be treated with the maximum dose of 1,200 mg daily (1.5 x 800 mg tablets) based on the average dose of 883 mg per day in the eslicarbazepine acetate trials. The manufacturer concluded, when considering dose-weighted average daily maintenance costs, that eslicarbazepine acetate was less expensive than either lacosamide or perampanel.

Key limitations in the manufacturer's submission included uncertainty regarding the assumption of clinical similarity between eslicarbazepine acetate and comparators due to limitations of the NMA, such as trial heterogeneity and wide credible intervals in terms of harms; absence of other, less expensive comparators used for adjunctive therapy in refractory partial-onset seizures; and uncertainty related to the proportion of patients in clinical practice who will use the 1,200 mg eslicarbazepine acetate dose.

If the assumption of clinical similarity is accepted, at the confidential submitted price of $[redacted] per tablet for eslicarbazepine acetate, assuming that 20.7% of patients will receive 1,200 mg (1.5 x 800 mg tablets), the dose-weighted average daily maintenance cost of eslicarbazepine acetate ($[redacted], excluding markup) is less expensive than dose-weighted average daily costs derived from the current list prices of both lacosamide ($7.06) and perampanel ($9.45). Over a full year, this difference would result in an estimated average per patient savings of $[redacted] and $[redacted] for eslicarbazepine acetate when compared with lacosamide and perampanel, respectively. If 2 x 600 mg tablets of eslicarbazepine acetate are used rather than 1.5 x 800 mg tablets, the daily cost for patients requiring 1,200 mg eslicarbazepine acetate ($[redacted] daily) is more expensive than the maximum dose of perampanel ($9.45 daily).

Eslicarbazepine acetate is more expensive than most other AEDs used in this population, such as lamotrigine ($0.37 to $1.85 daily), topiramate ($1.19 to $1.77 daily), gabapentin ($0.77 to $1.54 daily), and levetiracetam ($1.95 to $5.40 daily); however, its relative clinical efficacy, safety, and tolerability to these comparators are unknown. The use of eslicarbazepine acetate in combination with perampanel or lacosamide would be more costly than other combinations of AEDs.

Other Discussion Points:

- The chemical structure of eslicarbazepine acetate is similar to that of oxcarbazepine; however, there are no direct or indirect comparisons of these two drugs. At lower doses, treatment with oxcarbazepine is less costly than treatment with eslicarbazepine acetate.
- Patients with partial onset seizures progressing to generalized seizures may be less likely to benefit from the addition of eslicarbazepine. A subgroup analysis from one trial (study 304) suggested that patients already taking carbamazepine may also be less likely to benefit from the addition of eslicarbazepine acetate; however, the findings must be interpreted in light of the fact that sample sizes for each subgroup were relatively small.
- Significant central nervous system–related adverse events (nausea, vomiting, and somnolence) were observed in patients taking eslicarbazepine acetate in all four clinical trials.
- Study 303 had significant Good Clinical Practice compliance deficiencies and was not considered by Health Canada to be a pivotal trial.
- Patients in studies 301, 302, and 303, and the first 168 patients in Study 304, recorded a seizure event in a diary when a seizure occurred. As such, there was no means of differentiating whether the absence of a seizure entry for a particular day was due to non-occurrence of seizure or a seizure that was not recorded by the patient or caregiver. This likely resulted in some seizures being missed in the analyses.
- Eslicarbazepine acetate and carbamazepine belong to the same class of drugs and share a similar mechanism of action. Carbamazepine is associated with skin-related adverse events, which can range from mild skin rash to more serious skin reactions such as Stevens–Johnson syndrome. Eslicarbazepine acetate was developed as a safer alternative to carbamazepine. Due to limited long-term data, it is unclear if eslicarbazepine acetate could potentially cause severe skin reactions, but the possibility of such reactions exists.

- In the included trials, few patients reported cognitive disorder, disturbance in attention, or memory impairment as a treatment-emergent adverse event. However, it is uncertain whether eslicarbazepine acetate has advantages over other AEDs in this respect.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:
- There are no direct comparisons of eslicarbazepine acetate against other AEDs used for the treatment of refractory partial-onset seizures.
- The long-term efficacy and safety of eslicarbazepine acetate require further evaluation.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

March 18, 2015 Meeting

Regrets:

One CDEC member was unable to 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. CADTH has redacted the requested confidential information in accordance 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.