CADTH CANADIAN DRUG EXPERT COMMITTEE
FINAL RECOMMENDATION

PERAMPANEL
(Fycompa — Eisai Limited)
Indication: Epilepsy, Primary Generalized Tonic-clonic Seizures

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that perampanel be reimbursed for adjunctive therapy in the management of primary generalized tonic-clonic (PGTC) seizures in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy, if the following clinical criteria and conditions 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.
- Reduced price.

Reasons for the Recommendation:
1. One randomized controlled trial (RCT) (study 332 [N = 164]) demonstrated that treatment with perampanel resulted in statistically significant and likely clinically meaningful reductions in seizure frequency per 28 days compared with placebo.
2. At the submitted price [redacted] per day), the CADTH Common Drug Review (CDR) estimated that perampanel is associated with an incremental cost-utility ratio (ICUR) of $74,758 per quality-adjusted life-year (QALY) compared with other AEDs for adjunctive therapy in the management of PGTC seizures in adult patients with epilepsy; therefore, perampanel is not considered to be cost-effective at the submitted price.

Of Note:
1. CDEC noted that there is no evidence on the comparative benefits and risks of perampanel with alternative AEDs as adjunctive therapy in the management of PGTC seizures in adult patients with epilepsy.
2. CDEC noted that perampanel is one of 16 AEDs currently marketed in Canada; however, there remains a need for additional treatment options in patients with epilepsy who are not satisfactorily controlled with one or more AEDs.

Background:
Perampanel has a Health Canada indication as adjunctive therapy in the management of PGTC seizures in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy. Perampanel is an AED that is thought to be a selective, non-competitive antagonist of the ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptor on post-synaptic neurons. It is available as 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg tablets. The recommended dose of perampanel is 2 mg to 12 mg once per day orally and varies depending on the patient's concomitant use of enzyme-inducing AEDs.

Summary of CDEC Considerations:
The Committee considered the following information prepared by CADTH CDR: a systematic review of RCTs of perampanel and 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 key information provided by two patient groups (Epilepsy Nova Scotia and Epilepsy Toronto) that responded to the CDR call for patient input:

- The impacts of epilepsy can vary widely in terms of frequency, severity and duration; for some patients, epilepsy can have a significant impact on all aspects of 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 license. 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 not effective for all patients and some patients continue to have uncontrolled epilepsy despite treatment. Available drug therapies are limited by adverse effects, including cognitive disturbances, mood swings, depression, suicidal thoughts, dizziness, sexual difficulties, drowsiness and fatigue.
- Patient groups suggest that new treatments provide hope that those with refractory epilepsy will find a treatment with fewer adverse effects that will eliminate or reduce their number of seizures and improve their quality of life.

Clinical Trials
The systematic review included one double-blind randomized placebo-controlled trial (study 332) that examined the efficacy and safety of adjunctive perampanel (up to 8 mg per day) versus placebo for the treatment of refractory PGTC seizures in patients ≥ 12 years of age with idiopathic generalized epilepsy (N = 164). All patients were treated with stable doses of one to three approved AEDs and had at least three documented PGTC seizures during the eight weeks prior to randomization. The treatment duration was a four week titration period and a 13 week maintenance period. Those enrolled had a mean age of 28 years (85% ≥ 18 years of age), 56% were female, and had epilepsy, on average, for 17 years. Twelve per cent of patients in the placebo group and 17% in the perampanel group withdrew from the study early.

The key limitations of study 332 were the short duration of the study (17 weeks), small sample size, lack of active comparator, lack of randomized comparative data on the 10 mg and 12 mg dosages approved for use in Canada, and no control of multiplicity of statistical testing for secondary outcomes.

Outcomes

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

- Per cent change from baseline in the frequency of PGTC seizures and frequency of all seizure types per 28 days.
- Responder rate — defined as the percentage of patients who experienced a 50% or greater reduction from baseline in PGTC seizure frequency per 28 days during double-blind maintenance treatment.
- Seizure-free status — defined as PGTC seizure free during the maintenance period.
- Quality of life — measured using the Patient Weighted Quality of Life in Epilepsy (QOLIE)-31-P, a self-reported questionnaire comprised of 39 items that are assessed on a four to six-point Likert scale, and an overall score converted to a scale of 0 to 100, with higher scores reflecting higher quality of life and lower scores worse quality of life.
- Clinician's Global Impression of Change — measured using a questionnaire that assesses the patient's clinical status during the preceding four weeks using a seven-point Likert scale.

The primary outcome in study 332 was the percent change in PGTC seizure frequency per 28 days relative to baseline during the double-blind treatment phase.

Efficacy

- There were statistically significantly greater median per cent reductions in seizure frequency per 28 days with perampanel 8 mg compared with placebo. The median difference (95% confidence interval [CI]) in per cent change in seizure frequency was reported as follows:
    - PGTC seizures: -30.8%; 95% CI -45.5% to -15.2%
    - all-seizure types: -23.5%; 95% CI -40.7% to -8.5%
- Statistically significantly more patients showed a ≥ 50% reduction in PGTC seizure frequency in the perampanel versus placebo group (64% versus 40%, p=0.0019).
- More patients on perampanel were PGTC seizure-free than placebo (31% versus 12%); however, study 332 was not designed to test for differences in this outcome.
- Compared to the overall study population, the benefits in reduction of seizure frequency were similar for the adult subgroup (N = 139, representing 85% of the overall study population), which is the population approved for perampanel use in Canada.
- No clinically important differences were found in health-related quality of life based on the QOLIE-31-P.
- Clinician-rated Global Impression of Change showed few differences between treatment groups in the proportion of patients rated as improved, worsened or showing no change after 12 weeks of therapy.
- No data were available on the number of school or work days missed, an outcome which the patient group input identified as important.

Harms (Safety and Tolerability)

- In study 332, most patients reported one or more adverse events during the trial (perampanel 83%, placebo 72%).
- More patients stopped treatment due to adverse events in the perampanel group (11%) than in the placebo group (6%).

- Dizziness (32% versus 6%), fatigue (15% versus 6%), somnolence (11% versus 4%) and irritability (11% versus 2%) were reported more frequently in those receiving perampanel than placebo.
- More patients who received perampanel reported a > 7% increase in body weight (11% versus 4%) and aggression or hostility-related adverse events (19% versus 5%) compared with placebo.
- The frequency of serious adverse events was similar in the perampanel and placebo groups, 7% and 9%, respectively.

Cost and Cost-Effectiveness

The confidential submitted price for perampanel is [redacted]. At the recommended maintenance dose of 8 to 12 mg daily, perampanel costs [redacted] per day.

The manufacturer submitted a cost-utility analysis comparing perampanel added to background AED therapy to background AEDs alone in adult patients with PGTC seizures who are not satisfactorily controlled with existing therapy. The analysis was undertaken from the Canadian public payer perspective over a lifetime horizon, and was based on a Markov model comprised of four health states representing seizure frequency: 53+ seizures/year, 13-52/year, 1-12/year and seizure freedom. All patients started in the 53+ or 13-52 seizures/year states and moved between states based on treatment response (measured in terms of percent reduction in seizure frequency). Treatment response for the first 4 months was informed by the results of study 332, and extrapolated thereafter based on values from a longitudinal cohort study assessing the effects of treatment switching in patients with PGTC seizures with inadequate seizure control on existing therapy. Each state was associated with a utility weight, cost and risk of mortality. Utilities and estimates of resource use were based on values provided by European respondents to a survey examining the burden of PGTC seizures. Patients could die at any time due to all-cause mortality or mortality due to epilepsy, with mortality risk increasing with increasing seizure frequency.

The manufacturer reported that when added to background AEDs, the ICUR of perampanel was $47,159 per QALY compared to background therapy alone.

CDR noted a number of limitations with the manufacturer's analysis:

- Treatment response after the first model cycle was based on extrapolation using data from a cohort that was not comparable to the modelled patient population
- The distribution of baseline seizure frequencies did not reflect Canadian clinical practice
- Costs for perampanel in the model were based on a lower mean dose than was used in study 332
- Adverse events were not included in the model despite evidence that perampanel may be associated with a higher risk of some AEs compared with placebo
- Perampanel is compared to placebo in the analysis, whereas in clinical practice, other untried AEDs may be appropriate comparators to perampanel as adjunctive therapy for PGTC seizures. In the absence of direct or indirect comparative evidence, the comparative cost effectiveness of perampanel versus other AEDs as adjunctive therapy is unknown.

Based on CDR re-analyses to account for some of the above limitations (i.e., use of alternative assumptions around long-term treatment response, revised baseline seizure frequency

distribution, and corrected perampanel costs), perampanel was associated with an ICUR of $74,758 per QALY when compared with background therapy alone. A price reduction of over 20% would be needed for the ICUR of perampanel to fall below $50,000 per QALY. CDR noted that perampanel is more costly than all other AEDs except for lacosamide and eslicarbazepine.

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, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

March 16, 2016 Meeting

Regrets:
None

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.

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