Common Drug Review
Pharmacoeconomic Review Report

May 2016

Drug	Perampanel (Fycompa)
Indication	Indicated as adjunctive therapy in the management of partial-onset and primary generalized tonic-clonic (PGTC) seizures, in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy
Reimbursement Request	As per indication
Dosage Form(s)	2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg tablets
NOC Date	December 2015
Manufacturer	Eisai Limited.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

AE	adverse event
AED	anti-epileptic drug
CDR	CADTH Common Drug Review
ICUR	incremental cost-utility ratio
LY	life-year
ODB	Ontario Drug Benefit formulary
PGTC	primary generalized tonic-clonic seizure
QALY	quality-adjusted life-year
RR	relative risk

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	**Perampanel (Fycompa)**
Study Question	To examine the cost-effectiveness of using perampanel as an adjunctive therapy in the management of primary generalized tonic-clonic (PGTC) seizures in adult patients with epilepsy not satisfactorily controlled with conventional therapy in Canada.
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adult epilepsy patients with PGTC seizures not satisfactorily controlled with conventional therapy, defined as failing at least one anti-epileptic drug (AED)
Treatment	Perampanel 8 mg daily, adjunctive to background anti-epileptic drugs (AEDs, consisting of lamotrigine, valproic acid, levetiracetam, and topiramate)
Outcomes	Quality-adjusted life-years (QALYs) Life-years (LYs)
Comparator(s)	AEDs alone
Perspective	Canadian public payer (societal perspective considered as secondary analysis)
Time Horizon	Lifetime (50 years)
Results for Base Case	Perampanel + AEDs has an incremental cost-utility ratio (ICUR) of $47,159 per QALY versus placebo + AEDs.
Key Limitations	CADTH Common Drug Review (CDR) noted the following limitations: • Treatment response after the first model cycle is based on extrapolation using data from a cohort that is not comparable with the modelled patient population. • Distribution of baseline seizure frequencies does not reflect Canadian clinical practice. • Costs of perampanel in the model are based on a lower dose than what was used to establish efficacy in the trial. • Adverse events (AE) are not included in the model despite evidence that perampanel may be associated with a higher risk of some AEs (including dizziness, weight gain and aggression/hostility).
CDR Estimate(s)	• Based on analyses to address key limitations, CDR found perampanel adjunctive to background AEDs is associated with an ICUR of $74,758 per QALY when compared with AEDs alone from the public-payer perspective. • A price reduction of more than 20% would be necessary for perampanel to be cost-effective at a willingness-to-pay threshold of $50,000/QALY.

AE = adverse event; AED = anti-epileptic drug; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; LY = life-year; QALY = quality-adjusted life-year; PGTC = primary generalized tonic-clinic.

EXECUTIVE SUMMARY

Background

Perampanel (Fycompa) is a non-competitive agonist of the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor.[1] Perampanel is indicated as adjunctive therapy in the management of primary generalized tonic-clonic (PGTC) seizures in adult patients who are not satisfactorily controlled with conventional anti-epileptic drug (AED) therapy. The manufacturer submitted confidential prices of $[redacted] (2 mg), $[redacted] (4 mg), $[redacted] (6 mg) and $[redacted] (8 mg, 10 mg and 12 mg tablets). The recommended starting dose for most patients is 4 mg daily, titrated to a recommended maintenance dose of 8 mg to 12 mg daily according to individual patient response.[2] At the recommended maintenance dose of 8 mg to 12 mg daily, perampanel costs $[redacted] daily. This represents a [redacted]% reduction from the current list price of perampanel ($9.45 for all dosage forms) on the Ontario Drug Benefit (ODB) Formulary.[3]

Perampanel was previously reviewed by the CADTH Common Drug Review (CDR) in 2013 as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy not satisfactorily controlled with conventional therapy.[4] The Canadian Drug Expert Committee (CDEC) recommended perampanel be listed (with conditions and criteria) based on demonstrated reductions in seizure frequency compared with placebo and its lower price compared with lacosamide.

The manufacturer submitted a cost-utility analysis comparing perampanel added to background AEDs with AEDs alone among adult patients with PGTC seizures not satisfactorily controlled on AEDs. The analysis used a lifetime horizon and was undertaken from the Canadian public-payer perspective.[5] The manufacturer reported that, when compared with treatment with AEDs alone, perampanel has an incremental cost-utility ratio (ICUR) of $47,159 per quality-adjusted life-year (QALY).

Summary of Identified Limitations and Key Results

CDR noted several limitations of the manufacturer's economic submission. Modelling of long-term treatment efficacy relied on a longitudinal study by Neligan et al.[6] that considered a cohort that differed considerably from the one modelled in the submission. In particular, Neligan et al. assessed seizure response upon the addition of a previously unused AED among patients with uncontrolled epilepsy. They noted that introducing a new AED upon failure of previous treatment may result in better seizure control. By contrast, the manufacturer's model considers patients who start on adjunctive perampanel or AEDs alone. No treatment switches occur during the course of the model time horizon and it was not considered reasonable to assume that the favourable response observed by Neligan et al. upon addition of an unused AED can be applied to patients in the model. Further limitations included: the modelled population was more severe than what would be seen in Canadian clinical practice, which may serve to exaggerate treatment efficacy; the costs of perampanel in the model are based on a lower dose than was used to establish efficacy in the trial; and an inappropriate assumption in the model that perampanel was not associated with a higher risk of adverse events (AEs) versus placebo despite evidence from Study 332 (and other sources for doses higher than 8 mg/day) to the contrary.

Conclusions

When attempting to address the identified limitations considering alternative assumptions around long-term treatment response, severity of the patient cohort, and costs of perampanel, CDR estimated that the ICUR for perampanel + AED compared with AEDs alone was $74,758 per QALY.

CDR was unable to assess the impact of considering a higher risk of adverse events (AEs) with perampanel (as observed in Study 332), given how the manufacturer modelled AE; this would increase the ICUR even further. Considering CDR's base case, a price reduction of more than 20% would be required for the ICUR of perampanel to fall below $50,000 per QALY.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis based on a Markov model comparing perampanel added to background anti-epileptic drug (AED) therapy consisting of a basket of conventional AEDs with AED therapy alone among adult patients with primary generalized tonic-clonic (PGTC) seizures not satisfactorily controlled with AEDs.[5] The basket of AEDs considered as background therapy consisted of lamotrigine, valproic acid, levetiracetam, and topiramate. The cost of an "average" AED in the model was a reflection of the AEDs taken in Study 332 and the proportion of patients using each one. Each patient was on 1.87 AEDs as per mean usage in Study 332.[7] The model comprised four health states based on seizure frequency: 53 or more seizures/year, 13 to 52 seizures/year, 1 to 12 seizures/year and seizure freedom. The model cohort characteristics were assumed to be similar to the baseline characteristics of patients in the Study 332, with 55.6% females, average age of 30, and an initial seizure frequency of 13 to 52 seizures/year in 43.21% of patients and 53 or more seizures/year in 56.79% of patients. The base-case adopted a lifetime horizon (50 years) and used four-month cycles. The analysis was undertaken from the Canadian public-payer perspective.

Movement between health states was based on treatment response in terms of percentage reduction in seizure frequency from baseline (< 50% reduction, 50% to 74% reduction, 75% to 99% reduction and seizure freedom). Patients could maintain, lose, or gain treatment response as time progressed — e.g., a patient with an initial response of 50% to 74% reduction from baseline seizure frequency could maintain a 50% to 74% response, drop to < 50% reduction, or improve to the point of seizure freedom or 75% to 99% reduction from initial seizure frequency. Patients who experienced < 50% reduction in seizure frequency could enter a non-responder state characterized by increased seizure frequency (to the baseline rate) and maintenance therapy consisting of AED therapy without perampanel. The distribution of patients across seizure frequency states was updated in each cycle accordingly. In the first four-month cycle, treatment response in terms of per cent seizure reduction was based on observed values from the Study 332. Subsequent maintenance, loss, or gain of response was based on extrapolation using the results of a cohort study assessing seizure response to the addition of a previously unused AED among patients with refractory epilepsy.[6] Patients could die at any time, according to all-cause mortality risks from Statistics Canada. Mortality due to epilepsy was accounted for by applying relative risk (RR) for mortality (relative to the seizure-free subgroup). RRs of mortality for each health state were derived from a previous case-control study examining the incidence of sudden unexpected death due to epilepsy (SUDEP) among a cohort of Swedish patients.[8]

Patients incurred costs and utilities according to the seizure frequency states they passed through. Utilities were based on Short Form 6D (SF-6D) values from European respondents to Kantar Health's National Health and Wellness Survey examining the burden of PGTC seizures.[9] Estimates of resource use were obtained from the same survey and covered visits to health care providers, emergency room visits, and hospitalizations. Drug dosages were based on the World Health Organization Collaborating Centre for Drug Statistics Methodology's daily defined dose. The cost of perampanel treatment was calculated using the manufacturer's submitted price, while the costs of all other medications were obtained from the Ontario Drug Benefit (ODB) Formulary (2015).[3] Rates of background medication use were based on values observed in the Study 332. The cost of a visit to a general practitioner was obtained from the

2015 Ontario Schedule of Benefits.[10] The average cost of an emergency room visit for an epilepsy-related incident was taken from the Alberta Interactive Health Data Application.[11] The average cost of a hospitalization for an epilepsy-related incident was taken from the Canadian Institute for Health Information's Patient Cost Estimator.[12] All health care unit costs were inflated to 2015 Canadian dollars using the Canadian Consumer Prices Index for Health Care Services. The costs for adverse events (AEs) were not considered as the manufacturer posited that AEs did not differ appreciably between the perampanel and placebo arms in the Study 332. For the analysis from the societal perspective, productivity losses were based on an analysis of EU respondents to Kantar Health's National Health and Wellness Survey.[9]

2. MANUFACTURER'S BASE CASE

From the public-payer perspective, the manufacturer reported in its base-case analysis that perampanel is associated with a cost of $127,976, 15.23 life-years (LYs) and 9.56 quality-adjusted life-years (QALYs). When compared with AEDs alone, perampanel was $13,116 more costly and associated with 0.20 additional LYs and 0.28 additional QALYs, for incremental cost-effectiveness ratios (ICERs) of $66,938/LY and $47,159/QALY.

2.1 Summary of Manufacturer's Sensitivity Analyses

Among the manufacturer's sensitivity analyses, the number of hospitalizations per cycle for those in the 53 or more seizures/year state, dosage of background medications used, and RR of mortality for those in the 53 or more seizures/year state were all found to affect ICURs. Of these, the sensitivity analysis for number of hospitalizations for patients with 53 or more seizures/year demonstrated the largest impact on cost-effectiveness estimates, with ICURs from the public-payer perspective ranging from –$111 (adjunctive perampanel dominates AEDs alone) to $65,711 per QALY. It should be noted however that some of the values chosen as upper and lower bounds for the sensitivity analyses of these parameters lacked face validity (e.g., for hospitalizations per cycle, the base-case value was 0.4 while the lower bound assessed was 0.02, which amounts to only one hospitalization per year for every 16 to 17 patients experiencing 53 or more seizures/year).

The manufacturer reported the results of a probabilistic sensitivity analysis, in which there was a 50% chance that the ICUR for perampanel is less than $50,000 per QALY. Considering that the manufacturer's base-case ICUR is $47,159, the relatively low probability reflects significant uncertainty in the ICUR estimate.

3. LIMITATIONS OF MANUFACTURER'S SUBMISSION

- **Treatment response after cycle 1 is modelled based on extrapolation from a cohort that is not comparable to the Study 332 population:**
  Patient movement between seizure frequency states was based on per-cycle response to treatment (in terms of per cent seizure reduction); in each cycle, patients could either maintain treatment effect, experience a loss of efficacy or a gain in efficacy (e.g., experience seizure freedom or 75% to 99% reduction relative to baseline after an initial response of < 50% or 50% to 74%). This is problematic for a number of reasons:
  - Extrapolation of treatment effects was based on a longitudinal cohort study by Neligan et al.,[6] who assessed seizure response after addition of a previously unused AED among patients with

uncontrolled epilepsy. They noted that introducing new AEDs upon failure of previous treatment may result in better seizure control. By contrast, the manufacturer's model considers patients who start on adjunctive perampanel or AEDs alone. No treatment switches occur over the duration of the analysis except for the removal of perampanel in patients transitioning to maintenance therapy after non-response to perampanel. Therefore, it is unjustifiable to assume that the favourable responses tied to the addition of previously unused AEDs observed by Neligan et al. can be applied to patients in the model in the absence of switching. The clinical expert consulted by CDR also confirmed that it would be unlikely to observe a gain in efficacy with the same treatment if initial efficacy (in the first four to six months) was poor. The result of this limitation is that effectiveness (and thus cost-effectiveness) is likely overestimated.

- **Distribution of baseline seizure frequencies does not reflect Canadian clinical practice:**
  The initial distribution in the model was 43.21% of patients experiencing 13 to 52 seizures/year and 56.79% experiencing 53 or more seizures/year, based on Study 332. However, the Gupta et al. publication that was used to generate utilities and resource use estimates found that of those on two or more AEDs, only 19.3% had one or more seizure/week (corresponding to the 53 or more seizures/year group).[9] The clinical expert further noted that the Study 332 population was more severe than what might be seen in Canadian clinical practice and suggested a similar breakdown as Gupta et al. (30% with at least one/week, 70% with 13 to 52). Considering a more severe population in the model is likely to exaggerate the absolute clinical effectiveness (and cost-effectiveness) in terms of reduced seizure frequency of perampanel compared with AEDs alone beyond what would be seen in clinical practice.

- **Costs of perampanel in the model are based on a lower dose than what was used to establish efficacy in the trial:**
  It was observed that patients consumed background AEDs at 86% (on average) of the WHO-recommended dose.[13] This proportion was applied to the costs of AEDs to calculate costs of background therapy. While this was considered acceptable, the manufacturer applied a similar reduction to the cost of the 8 mg daily dose of perampanel, even though the mean and median doses of perampanel taken in the Study 332 were 7.5 mg and 8 mg daily, respectively.[14] As such, the average patient in perampanel arm of the model incurred the costs of 6.88 mg of perampanel while receiving the benefits of 7.5 mg to 8 mg. This would tend to improve the apparent cost-effectiveness of perampanel.

- **Inappropriate handling of adverse events:**
  The manufacturer omitted consideration of AEs from its evaluation, noting that the incidence of AEs was similar between the perampanel and placebo arms of the Study 332.[7] However, this claim is of questionable validity.
  - As per Table 12 of CDR Clinical Review, a higher proportion of patients in the perampanel group reported one or more AEs (83% versus 72% in the placebo arm), and there was a markedly higher incidence of dizziness (32% versus 6%) and fatigue (15% versus 6%). There was also a higher incidence of central nervous system-related AEs in the perampanel group (e.g., in Table 14 of the CDR Clinical Review, 19% of patients experienced aggression or hostility in the perampanel arm compared with 5% in the placebo arm). These data suggest that the assumption in the model of an equivalent incidence of AEs between perampanel and placebo may be inappropriate, although non-serious AEs are not expected to have an appreciable impact on costs or ICURs. The incidence of serious AEs was noted to be similar between the perampanel and placebo arms of the Study 332.[7]

- While the 8 mg/day dose was assessed during the double-blind period of the Study 332, patients were up-titrated to 12 mg daily at the investigator's discretion during the open-label extension study, and 90% of patients in the extension study used doses of more than 8 mg/day.[15] As noted in the CDR review of perampanel for the treatment of partial-onset seizures, a higher proportion of patients discontinued treatment at the 12 mg dose due to unacceptable side effects compared with lower doses.[4] If withdrawals due to AEs are more likely in the perampanel arm with 10 mg/12 mg dosing compared with AEDs alone, this would likely contribute to poorer seizure control than modelled in the analysis, thereby reducing the apparent effectiveness and cost-effectiveness of perampanel.

As such, the incidence of AEs is likely underrepresented in the model, and the safety profile of the Health Canada–approved 10 mg and 12 mg doses is uncertain. The increased incidence of AEs in the perampanel arm could result in additional costs; therefore, the failure to consider AEs likely overestimates the cost-effectiveness of perampanel.

- **Choice of comparator:**
  Perampanel is compared with placebo in the model, both added to a basket of background AEDs. In effect, the model estimates the cost-effectiveness of perampanel for patients who have inadequate control despite trials of all of the background treatments. However, in clinical practice, the composition of this basket depends on patient-specific medication history. As such, any of the given medications composing background treatment in the model (lamotrigine, valproic acid, levetiracetam, and topiramate) could be appropriate comparators for perampanel if they have not been used previously. In the absence of direct or indirect comparative evidence for perampanel versus these agents, it is difficult to speculate what the comparative cost-effectiveness would be. If similar efficacy is assumed between perampanel and the other AEDs, the analysis reduces to a cost-minimization exercise, and perampanel is the most costly of the comparators. However, the newer AEDs lacosamide and eslicarbazepine, which may be used off-label for PGTC seizures, according to the clinical expert consulted by CDR, are more costly than perampanel.

3.1 CADTH Common Drug Review Reanalyses

To account for the limitations identified above, the following analyses were undertaken:

1. **Initial distribution of patients**
   Based on Gupta et al.[9] and input from the clinical expert, the initial distribution of patients between seizure frequency states was changed from 43.21% to 70% for 13 to 52 seizures/year, and from 56.79% to 30% for 53 or more seizures/year.

2. **Alternative treatment response assumptions**
   To account for the limitation related to modelling of treatment response, patients were assumed to maintain their initial response to therapy or experience loss of treatment efficacy, but could not subsequently experience a gain in treatment effect.

3. **Dosage costing**
   Patients were assumed to incur the costs of 7.5 mg perampanel daily on average (as per the Study 332)[14] as opposed to the costs of 6.88 mg perampanel assumed in the manufacturer's base case.

CDR was unable to assess the limitation relating to the excluded costs of AEs as the model did not permit inclusion of such costs.

TABLE 2: CDR BASE CASE

Scenario		ICUR ($ per QALY) for Perampanel Versus AEDs Alone
	Manufacturer's base case	**$47,159**
1	Initial distribution	$53,521
2	Alternative treatment response assumptions	$57,615
3	Corrected costs of perampanel	$53,307
1–3	**CDR base case**	**$74,758**

AED = anti-epileptic drug; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

CDR Price-Reduction Analysis

When considering the CDR base case, a reduction of more than 20% in price would be necessary for the ICUR of perampanel to fall below $50,000 per QALY (Table 3).

TABLE 3: CDR RE-ANALYSIS OF PRICE-REDUCTION SCENARIOS

ICURs for Perampanel Versus AEDs Alone		
Price	**Base-Case Analysis Submitted by Manufacturer**	**Re-analysis by CDR**
Submitted ($[redacted]/8 mg tablet)	$47,159	$74,758
10% reduction ($[redacted]/8 mg tablet)	$40,336	$64,621
20% reduction ($[redacted]/8 mg tablet)	$33,514	$54,484
30% reduction ($[redacted]/8 mg tablet)	$26,691	$44,347

AED = anti-epileptic drug; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio.

4. ISSUES FOR CONSIDERATION

The consulting clinical expert noted that perampanel's once-daily dosing may be an advantage as adherence with AED therapy is often suboptimal among patients with epilepsy.

The clinical expert further indicated that perampanel, like other AEDs, is likely to be used in children despite the lack of an approved indication for this population. Therefore, the limited availability of data in pediatric patients could be considered a limitation.

4.1 Patient Input

Feedback was received from Epilepsy Nova Scotia and Epilepsy Toronto. Epilepsy was noted to have a significant impact on all aspects of life. The activities of daily living may be affected considerably (including the ability to operate motor vehicles). Issues of stigma contribute to difficulties in social functioning. Professional and educational development is also negatively affected and may contribute to loss of independence. The burden extends to family and friends in terms of heighted anxiety, financial concerns, and need for informal caregiving. The effect of epilepsy on patient well-being was adequately accounted for in the model by inclusion of quality-of-life weights that differed by disease severity. As well, a secondary analysis from the societal perspective that accounted for lost productivity was reported by the manufacturer.

Patients noted that the adverse effects of AEDs are considerable, and can be detrimental to the patient's well-being and their personal relationships. Furthermore, in approximately 30% of patients, seizures remain uncontrolled despite treatment. Patient groups anticipated that the availability of a novel treatment option may be useful for those who have failed to experience remission so far. One patient had experience with perampanel and commented favourably on the once-daily dosing. Seizures responded rapidly and the patient reported being seizure-free for two years. Adverse effects reported by the patient included dizziness and sleepiness; both were considered acceptable as the drug was taken before bed. The impact of AEs on costs and quality of life were not considered in the manufacturer's model, which was noted as a significant limitation.

5. CONCLUSIONS

At the submitted confidential price of perampanel, the manufacturer estimated a base case ICUR of $47,159 per QALY for perampanel + AED compared with AED alone. The manufacturer's submission was found to have several limitations; most notably the modelling of long-term treatment response was based on extrapolation from a study describing a markedly different clinical scenario compared with the decision problem. When considering alternative assumptions around long-term treatment response and baseline severity of the patient cohort, CDR estimated that the ICUR increased to $74,758 per QALY. Due to the structure of the model, CDR was unable to incorporate AEs; however, the increased incidence of AEs in the perampanel arm of Study 332 suggests that the ICUR for perampanel could be even higher than the CDR base case. Based on the CDR base case, a price reduction of 20% or greater is necessary for the ICUR of perampanel to fall below $50,000 per QALY.

APPENDIX 1: COST COMPARISON

The comparators presented in the Table 4 have been deemed to be appropriate by the clinical expert consulted by CDR. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

TABLE 4: COST COMPARISON TABLE FOR ANTI-EPILEPTIC DRUGS FOR THE TREATMENT OF PRIMARY GENERALIZED TONIC-CLONIC SEIZURES

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Dose	Daily Cost ($)	Annual Cost ($)
Perampanel (Fycompa)	**2 mg 4 mg 6 mg 8 mg 10 mg 12 mg**	**Tablet**	[redacted][a]	**4 mg to 12 mg once daily[b]**	[redacted] – [redacted]	[redacted] **to**
Carbamazepine (Tegretol, generics)	200 mg 100 mg 200 mg 200 mg 400 mg	Tablet Chewtabs Chewtabs CR tablet CR tablet	0.1540 0.0380 0.0749 0.0930 0.1859	800 mg to 1,200 mg in 2 to 4 divided doses	0.62 to 0.92 0.30 to 0.45 0.37 to 0.56	225 to 337 109 to 164 136 to 204
Clobazam (Frisium, generics)	10 mg	Tablet	0.1098	5 mg to 80 mg	0.05 to 0.88	20 to 321
Divalproex sodium (Epival, generics)	125 mg 250 mg 500 mg	EC tablet EC tablet EC tablet	0.0724 0.1301 0.2604	1,000 mg to 4,000 mg[c] in divided doses	0.52 to 2.08	190 to 760
Gabapentin (Neurontin, generics)	100 mg 300 mg 400 mg 600 mg 800 mg	Capsule Capsule Capsule Tablet Tablet	0.0749 0.1821 0.2171 0.3256[d] 0.4341[d]	900 mg to 1,800 mg in 3 divided doses	0.55 to 0.98	199 to 357
Lamotrigine (Lamictal, generics)	25 mg 100 mg 150 mg	Tablet	0.0936 0.3735 0.5505	100 mg to 500 mg in 2 divided doses	0.37 to 1.85	137 to 675
Levetiracetam (Keppra, generics)	250 mg 500 mg 750 mg	Film-coated tablet	0.8000[d] 0.9750[d] 1.3500[d]	1,000 mg to 3,000mg in 2 divided doses	1.95 to 5.40	712 to 1,971
Phenobarbital (generics)	15 mg 30 mg 60 mg 100 mg	Tablet	0..0927[d] 0.1103[d] 0.1496[d] 0.2048[d]	50 mg to 100 mg two to 3 times daily	0.20 to 0.61	75 to 224
Phenytoin sodium (Dilantin, generics)	30 mg 50 mg 100 mg	Capsule Tablet Capsule	0.0560 0.0783 0.0792	300 mg to 600 mg daily or in 2 or 3 divided doses daily	0.24 to 0.48	87 to 173

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Dose	Daily Cost ($)	Annual Cost ($)
Topiramate (Topamax, generics)	25 mg 100 mg 200 mg	Tablet	0.3128 0.5929 0.8854	200 mg to 400 mg in 2 divided doses	1.19 to 1.77	43 to 646
Valproic acid (generics)	250 mg 500 mg	Capsule Caplet	0.1366 0.4125	1,000 mg to 4000 mg[c] in divided doses	0.55 to 3.30	199 to 1,204
Vigabatrin (Sabril)	500 mg 0.5 g	Tablet Sachet	0.9110 0.9110[d]	2,000 mg to 3,000 mg in 2 divided doses	3.64 to 5.47	1,330 to 1,995

CR = controlled release; EC = enteric coated.
All prices from Ontario Drug Benefits Formulary (December 2015) unless otherwise indicated.[3]
[a] Manufacturer's confidential submitted price. Note that perampanel is currently listed on the Ontario Drug Benefit Formulary at a price of $9.4500 for all dosage forms.
[b] Initial dose is 4 mg in the presence of enzyme-inducing anti-epileptic drugs (AEDs; e.g., carbamazepine, oxcarbazepine, phenytoin) with dose increases in increments of 2 mg no more frequently than at one-week intervals to a maximum of 12 mg/day. In the absence of enzyme-inducing AEDs, initial dose is 2 mg/day, with dose increases of 2 mg increments no more frequently than at two-week intervals up to a dose of 8 mg/day, or 12 mg/day if well tolerated but lacking clinical response.[2]
[c] Initial dose 15 mg/kg/day, maximum dose 60 mg/kg/day, doses more than 250 mg/day should be divided. Daily dose in table based on 60 kg to 74.9 kg person.[16,17]
[d] Saskatchewan Formulary (December 2015).[18]

TABLE 5: COST COMPARISON TABLE FOR OTHER ANTI-EPILEPTIC DRUGS THAT MAY BE USED IN CLINICAL PRACTICE FOR THE TREATMENT OF PRIMARY GENERALIZED TONIC-CLONIC SEIZURES BUT ARE NOT INDICATED FOR THE CONDITION

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Dose	Daily Cost ($)	Annual Cost ($)
Eslicarbazepine (Aptiom)	200 mg 400 mg 600 mg 800 mg	Tablet	9.5600	800 mg to 1200 mg once daily[a,b]	9.56 to 14.34	3,489 to 5,234
Lacosamide (Vimpat)	50 mg 100 mg 150 mg 200 mg	Film-coated Tablet	2.5250 3.5000 4.7050 5.8000	200 mg to 400 mg in 2 divided doses[c]	7.00 to 11.60	2,555 to 4,234
Oxcarbazepine (Trileptal, generics)	150 mg 300 mg 600 mg	Tablet Tablet Tablet	0.6209[d] 0.9102[d] 1.8204[d]	600 mg to 2,400 mg in 2 divided doses	1.82 to 7.28	664 to 2,658
Primidone (Mysoline, generics)	125 mg 250 mg	Tablet	0.0553 0.0870	1,000 mg in 4 daily doses	0.35	127

All prices from Ontario Drug Benefits Formulary (December 2015) unless otherwise indicated.[3]
[a] 1,200 mg dose assumes the splitting of 800-mg tablets (1.5 tablet) as per product monograph.[19]
[b] Initial dose is 400 mg daily, increasing to 800 mg after one to two weeks. Some patients may require an increase to 1,200 mg daily if required after at least one week on 800 mg dose.[19]
[c] Initial dose is 50 mg twice daily, increasing by 50 mg twice daily each week until maintenance dose reached based on response and tolerability.[20]
[d] Saskatchewan Formulary (December 2015).[18]

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 6: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS PERAMPANEL RELATIVE TO AEDS?

Adjunctive Perampanel Versus AEDs Alone	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone					X	
Clinical Outcomes		X				
Quality of life		X				
Incremental cost-effectiveness ratio or net benefit calculation	$47,159 per QALY $66,938 per life-year					

AED = anti-epileptic drug; NA = not applicable; QALY = quality-adjusted life-year.

The above is based on the manufacturer's base case.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 7: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments *Reviewer to provide comments if checking "no"*	The model structure was unintuitive — use of individual-level patient data would have allowed the disease process to be represented solely by seizure frequency states without requiring separate states for treatment response. There were significant limitations associated with the use of Neligan et al.[6] to inform long-term treatment efficacy.		
Was the material included (content) sufficient?	X		
Comments *Reviewer to provide comments if checking "poor"*	None		
Was the submission well organized and was information easy to locate?	X		
Comments *Reviewer to provide comments if checking "poor"*	None		

TABLE 8: AUTHORS INFORMATION

Authors of the Pharmacoeconomic Evaluation Submitted to CDR
☐ Adaptation of Global model/Canadian model done by the manufacturer
☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer
☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer
☐ Other (please specify)

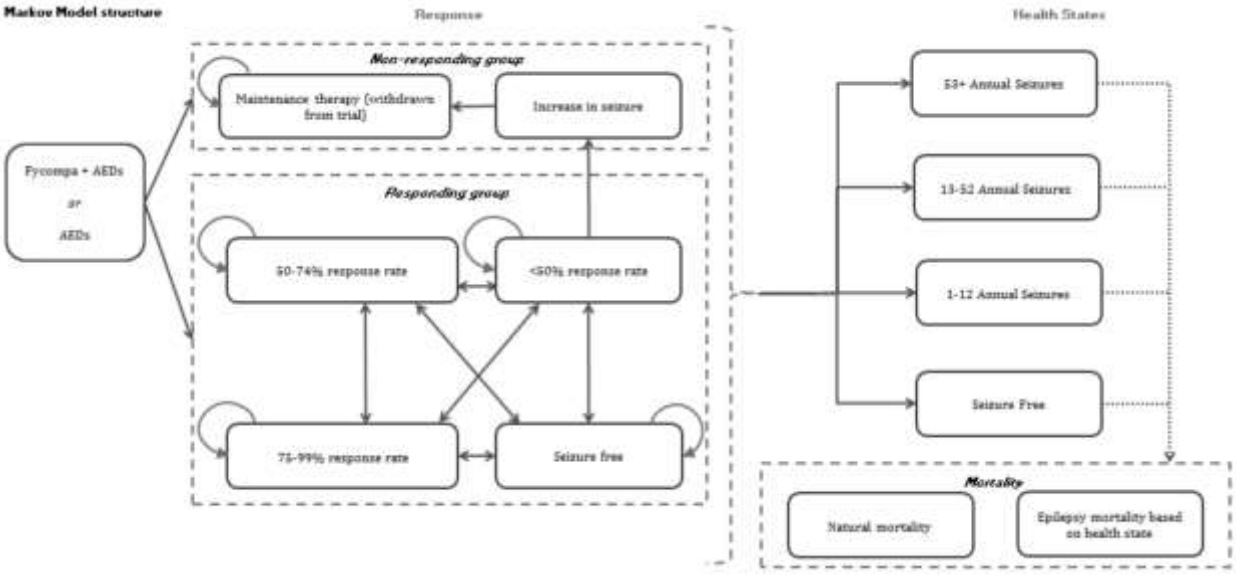
	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document		X[a]	
Authors had independent control over the methods and right to publish analysis	X		

[a] The report included an unsigned note indicating that "the authors are in full agreement with the entire document."

APPENDIX 4: REVIEWER WORKSHEET

FIGURE 1: MANUFACTURER'S MODEL STRUCTURE

Manufacturer's Model Structure



AED = anti-epileptic drug.
Source: Manufacturer's economic submission.[5]

TABLE 9: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	Efficacy was measured in terms of percentage reduction in seizure frequency, e.g., < 50%reduction, 50% to 74%, 75% to 99% and complete seizure freedom. These relative reductions were applied to the baseline frequency of seizures to determine seizure burden after treatment response. Efficacy values for cycle 1 (the first four months) were obtained from the Study 332.[7] Treatment response thereafter was based on extrapolation from a cohort study by Neligan et al. investigating seizure response to the addition of previously unused AEDs among patients with refractory epilepsy.[6]	Appropriate for cycle 1. Subsequent extrapolation based on Neligan et al. study is problematic. Neligan et al. assessed seizure response to the addition of newly added and previously unused AEDs among refractory patients. The model did not consider treatment switches (except for non-responders who stopped using perampanel without adding a new AED). As such, estimates of efficacy are likely overstated since patients incur positive seizure response without making use of new AEDs or treatment switching.
Natural history (Patient severity)	Initial distribution of patients to seizure frequency states was based on the proportions observed in Study 332[7] with 43.21% of patients initially experiencing 13 to 52 seizures/year and 56.79% experiencing 53 or more seizures/year.	This likely reflects a more severe population than would be seen in Canadian clinical practice. Adjusted in CDR's base case based on the values provided by Gupta et al.[9] (19.3% experiencing 53 or more seizures/year, 80.7% experiencing 13 to 52/year). This was confirmed as appropriate by the clinical expert.
Utilities	Based on SF-6D utilities provided by European patients to Kantar Health's National Health and Wellness Survey examining the burden of PGTC seizure.[9]	Utilities were noted to be low (e.g., the utility of seizure freedom was 0.71) and had questionable face validity in some instances (those experiencing 1 to 12 seizures per year had the same utility as those experiencing 13 to 52). Use of US values in place of EU values affected ICURs minimally.

Data Input	Description of Data Source	Comment
Resource use	The basket of drugs comprising background treatment was based on what was used in the Study 332. The "average" AED in the model was based on a weighted average of the drugs used in the Study 332. Patients took 1.87 AEDs on average and were observed to be taking 86% of the WHO-recommended dosage on average; costs were adjusted for observed adherence. Perampanel use was based on the recommended dose of 8 mg daily with the same adjustment for adherence applied to the cost of perampanel, even though the calculated dose did not accord with the mean dose observed in the clinical study report for the Study 332.[14] Use of non-drug medical resources: based on resource use among European respondents to Kantar Health's National Health and Wellness Survey examining the burden of PGTC seizure[9]	Cost adjustment of perampanel was unjustified and was corrected in the CDR base case. The basket of other AEDs was confirmed as appropriate by clinical expert.
AEs (Indicate which specific AEs were considered in the model)	Costs (and any potential disutilities) associated with AEs were not considered in the manufacturer's model. This was justified by claiming that AEs differed minimally between treatments.	Likely inappropriate. The incidence of AEs is likely underrepresented in the model. Further, the safety profile of the Health Canada–approved 10 mg and 12 mg doses is uncertain. The increased incidence of AEs in the perampanel arm could result in additional costs; therefore, the failure to consider AEs likely overestimates the cost-effectiveness of perampanel.
Mortality	General mortality: Statistics Canada life tables. Epilepsy specific mortality due to SUDEP: a case-control study undertaken in Sweden informed RRs for each seizure frequency state compared to seizure-free mortality.[8]	Confirmed as appropriate by clinical expert.
Productivity loss	Based on EU respondents to Kantar Health's National Health and Wellness Survey examining the burden of PGTC seizure.[9]	Unclear whether European estimates of productivity loss are applicable to the Canadian context.

Data Input	Description of Data Source	Comment
Costs		
Drug	AED background therapy: composition of basket from Study 332, cost of comparators from ODB formulary, adjusted for observed adherence (patients took, on average, 86% of the WHO-recommended dose). Perampanel: drug costs were obtained from the manufacturer's confidential submitted price.	Appropriate. While lower-cost alternatives such as carbamazepine and phenytoin were not considered, inclusion of these alternatives failed to affect ICURs appreciably.
Administration	No administration costs considered.	Appropriate.
Event	Doctor visits: The cost of a visit to a GP was obtained from the 2015 Ontario Schedule of Benefits.[10] The average cost of an emergency room visit for an epilepsy-related incident was taken from the Alberta Interactive Health Data Application.[11] Hospitalization for epilepsy-related incident: Canadian Institute for Health Information's Patient Cost Estimator.[12]	Appropriate.
AEs	Costs of AEs not considered.	This is inappropriate, given both the higher incidence of AEs in the perampanel arm and the lack of double-blind data on the 10 mg and 12 mg doses; for the partial-onset seizure indication, incidence of AEs and withdrawals due to AEs were noted to increase a dose-dependent fashion.[4]
Health state	Each seizure frequency state had a specific rate of doctor's visits, ER visits and hospitalizations.	Appropriate as per clinical expert.
Indirect costs	Average productivity per person was taken from the Organization for Economic Cooperation and Development and adjusted to 2015 Canadian dollar values using the Consumer Price Index.	Appropriate.

AE = adverse event; AED = anti-epileptic drug; CDR = CADTH Common Drug Review; GP = general practitioner; ER = emergency room; ICUR = incremental cost-utility ratio; ODB = Ontario Drug Benefit; PGTC = primary generalized tonic-clonic; RR = relative risk; SUDEP = sudden unexpected death in epilepsy; WHO = World Health Organization.

TABLE 10: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Efficacy of AEDs (including perampanel) among patients in Study 332 reflective of efficacy among Canadian patients with PGTC seizures.	Uncertain. The patient cohort studied in trial 332 was more severe than would be expected in Canadian clinical practice. As a result, treatment efficacy in the trial may be overstated.
Long-term treatment efficacy as informed by Neligan et al.[6] can reasonably inform long-term efficacy of treatment in the model.	Inappropriate. Neligan assesses treatment response to the addition of previously unused AEDs. The current model assumes that these treatment responses are applicable to an unchanging treatment regimen.
Mortality risks from Nilsson et al.'s Swedish cohort study[8] reflect Canadian mortality risk.	In the absence of current Canadian data, the clinical expert noted that the results had face validity.
Patients who become non-responders and experience increased seizures go to maintenance therapy and remain there.	In practice patients will move to an unused AED.
Where both EU and US results were available for utilities and resource use estimates, the EU estimates were more applicable to the Canadian context.	Unclear whether appropriate although CDR notes a paucity of data in this regard. The use of US values from Gupta et al.[9] did not appreciably change ICURs.
Adverse events were not considered as they were assumed to differ minimally between adjunctive perampanel and AEDs alone.	Likely inappropriate.
Composition of AED basket.	Acceptable. While lower-cost alternatives such as carbamazepine and phenytoin were not considered (confirmed as appropriate comparators by NICE, Ontario epilepsy guidelines and clinical expert),[21,22] CDR found that their inclusion did not appreciably impact ICURs.
Resource use was related to seizure frequency.	Appropriate.

AED = anti-epileptic drug; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; NICE = UK National Institute for Health and Care Excellence; PGTC = primary generalized tonic-clonic.

Manufacturer's Results

The manufacturer reported in its base case that perampanel is associated with a cost of $127,976, 15.23 life-years (LYs) and 9.56 quality-adjusted life-years (QALYs). When compared with anti-epileptic drugs (AEDs) alone, perampanel was $13,116 more costly and associated with 0.20 additional LYs and 0.28 additional QALYs, for incremental cost-effectiveness ratios of $66,938/LY and $47,159/QALY.

The manufacturer also undertook an analysis from the societal perspective, incorporating indirect costs and reporting that perampanel dominated the use of AEDs alone (i.e., was less costly and more

CADTH Common Drug Review Reanalyses

CDR conducted analyses on the following:

1. Initial distribution of patients was set to values from Gupta et al. (confirmed as appropriate by clinical expert) to correct for the higher severity of the modelled cohort compared with the likely severity distribution in Canadian clinical practice.
2. Alternative assumptions around treatment response were used to correct for use of Neligan et al.[6]
3. Dosage of perampanel was set to mean observed in Study 332.

The inclusion of adverse events (AEs) was not evaluated, as the model did not allow insertion of AE costs.

TABLE 11: CDR REANALYSES

		Cost Perampanel ($)	Cost AEDs ($)	Incremental Cost ($)	QALYs Perampanel	QALYs AEDs	Incremental QALYs	ICUR ($)
	Mfr. base case	127,976	114,861	13,116	9.56	9.28	0.28	47,159
1	Distribution	126,977	113,790	13,187	9.81	9.57	0.28	53,521
2	Natural history	128,501	116,474	12,028	9.40	9.19	0.21	57,615
3	Dosage	129,686	114,861	14,825	9.56	9.28	0.28	53,307
4 (1–3)	CDR base case	129,018	115,394	13,624	9.67	9.49	0.18	74,758

AE = adverse events; AED = anti-epileptic drug; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

CDR also undertook price-reduction analyses (Table 3), finding that price reductions of more than 20% would be necessary in CDR's base case to be cost-effective at a willingness-to-pay threshold of $50,000 per QALY.

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