



Common Drug Review

Pharmacoeconomic Review Report

May 2016

Drug	eslicarbazepine acetate (Aptiom) oral tablets
Indication	Adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy who are not satisfactorily controlled with conventional therapy.
Listing request	As per indication
Manufacturer	Sunovion Pharmaceuticals Canada Inc.

Eslicarbazepine acetate (Aptiom) Common Drug Review Pharmacoeconomic Report was prepared using PharmaStat data from IMS Health Canada Inc. The analyses, conclusions, opinions and statements expressed are those of CADTH and not those of IMS Health Canada Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in Neurology who provided input on the conduct of the review and the interpretation of findings.

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

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ABBREVIATIONS

AED	antiepileptic drug
ESL	eslicarbazepine acetate
NMA	network meta-analysis
POS	partial-onset seizure

SUMMARY

Background

Eslicarbazepine acetate (ESL; Aptiom) is indicated as adjunctive therapy in the treatment of partial-onset seizures (POS) in patients with epilepsy who are not satisfactorily controlled with conventional therapy. It is not indicated for a pediatric population. ESL is available in 200 mg, 400 mg, 600 mg, and 800 mg tablets at a confidential price of [REDACTED] per tablet for all strengths. The recommended starting dose of ESL is 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. The dose may be increased to a maximum of 1,200 mg once daily (administered as one and a half 800 mg tablets).¹ Consequently, the daily cost of ESL ranges from [REDACTED] to [REDACTED].

Summary of the Economic Analysis Submitted by the Manufacturer

The manufacturer submitted a cost-minimization analysis² comparing ESL with lacosamide and perampanel when used as adjunctive therapy to concomitant antiepileptic drugs (AEDs) for the treatment of adults with refractory POS who are not satisfactorily controlled on conventional therapy, which is defined for the cost-minimization analysis as epileptic seizures that are not controlled on a stable dose of at least one AED to reflect the population of the ESL pivotal trials.³⁻⁶ 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 between all three comparators was based on the results of a manufacturer-funded unpublished network meta-analysis (NMA) (see CADTH Common Drug Review [CDR] Clinical Review Report, Appendix 7). Costs for lacosamide and perampanel were derived using Ontario Drug Benefit Formulary list prices plus an 8% markup, and dose-weighted using IMS PharmaStat Ontario public data for units reimbursed from January to May 2014. Costs for ESL were derived using the manufacturer's confidentially submitted price of [REDACTED] per tablet plus an 8% markup, and by assuming that 20.7% of patients would be treated with the maximum dose of 1,200 mg daily (1.5 tablets), based on the average dose of 883 mg per day in the ESL trials.^{7,8}

The manufacturer concluded that at a dose-weighted average daily maintenance cost of [REDACTED] (including markup), ESL was less expensive than either lacosamide (dose-weighted average daily cost of \$7.62) or perampanel (dose-weighted average daily cost of \$10.21).

Key Limitations

Uncertainty in the Assumption of Clinical Similarity

There are no head-to-head trials comparing ESL to active comparators in patients with epilepsy with POS inadequately controlled with conventional AEDs. In the submitted NMA, no significant differences were found in efficacy, discontinuation, treatment-emergent adverse events (TEAEs), TEAEs leading to discontinuation, or serious adverse events between ESL, lacosamide, and perampanel (see CDR Clinical Review Report, Appendix 7). However, limitations in the NMA, such as heterogeneity across included trials (patient's characteristics, titration, and maintenance period) increase the uncertainty in the clinical similarity of ESL compared with lacosamide or perampanel. Should the average doses of ESL, lacosamide, and perampanel used in clinical practice vary from the clinical trials, the NMA findings might not be generalizable to the Canadian setting.

Appropriate Comparators Omitted

The manufacturer compared ESL with lacosamide and perampanel but did not include any other drugs (e.g., lamotrigine, topiramate, gabapentin, levetiracetam) used in Canada as adjunctive therapy in refractory POS. These drugs are all less expensive than ESL, but their safety, tolerability, and efficacy relative to ESL are unknown.

Uncertain Dose Usage

There is uncertainty in the proportion of patients in clinical practice who will use ESL at a daily dose of 1,200 mg versus 800 mg. CDR analyses, using varying proportions of patients on 1,200 mg (versus 20.7% as assumed by the manufacturer), showed that ESL remains a cost saving under all reasonable dose-utilization assumptions, though the amount of potential savings varies considerably (Table 8).

Titration Period and Dose Variations Not Considered

The analysis is based on a one-day time frame and assumes patients receive a maintenance dose, which does not allow the impact of potential different titration durations to be assessed. ESL,¹ lacosamide,⁹ and perampanel¹⁰ require a titration phase, and the maintenance dose will vary based on an individual's tolerance. However, given that perampanel has a flat price, this would only impact the comparison with lacosamide. Further, given the relatively short duration of the titration phase, and the fact the utilization data showed that 71% of claims for lacosamide were for doses of 50 mg or 100 mg, the conclusion of cost savings with ESL versus its comparators is unlikely to change.

Issues for Consideration

Price Variability

To assess the impact of potential price fluctuations, differences in pricing across jurisdictions, and the possible availability of generic versions of comparators within the next several years, CDR conducted analyses exploring the relative savings or additional cost of ESL compared with perampanel and lacosamide in various price-reduction scenarios (Appendix 1). Results show that, at the submitted price, ESL remains a cost saving compared with lacosamide and perampanel up to a price reduction of these drugs of greater than [REDACTED].

Alternate 1,200 mg Dosing

While the ESL product monograph¹ recommends that the 1,200 mg daily dose be administered as one and one-half 800 mg tablets (daily cost: [REDACTED]), it is possible that some patients will receive this dose as two 600 mg tablets daily ([REDACTED]), which would be more expensive than the daily cost of all doses of perampanel (\$9.45).

Combination Therapy With Perampanel or Lacosamide

The clinical expert consulted by CDR noted that in some situations, physicians may consider combining ESL with perampanel or lacosamide rather than substituting one for another. This combination would be more costly than other combinations of AEDs.

Comparators' Listing Restriction

Under most jurisdictional formularies, lacosamide and perampanel reimbursement is restricted to patients with refractory partial-onset seizures taking at least two other AEDs and who have had an inadequate response or who have demonstrated intolerance to other less expensive AEDs.

Pediatric Use

Like lacosamide⁹ and perampanel,¹⁰ ESL¹ is not indicated for pediatric patients. However, according to the clinical expert consulted by CDR, lacosamide is frequently used in children and adolescents with refractory POS, and perampanel is beginning to be used for this population as well. Thus, it is likely that ESL will also be used in pediatric patients as clinicians gain familiarity with it.

Results/Conclusions

If the assumption of clinical similarity is accepted, at the confidentially submitted price of [REDACTED] per tablet, the dose-weighted average daily maintenance cost of ESL ([REDACTED], excluding markup) is less expensive than the dose-weighted average daily costs derived from the current list prices of both lacosamide (\$7.06) and perampanel (\$9.45) for the treatment of patients with POS with epilepsy who are not satisfactorily controlled with conventional therapy. Over a full year, this difference would result in an estimated average per-patient saving of [REDACTED] and [REDACTED] if ESL were used rather than lacosamide and perampanel, respectively. ESL is more expensive than most other comparators appropriate in this population (e.g., lamotrigine, topiramate, gabapentin, levetiracetam); however, its relative clinical safety, tolerability, and efficacy relative to these comparators is unknown. The combination of ESL with perampanel or lacosamide would be more costly than other combinations of AEDs.

Cost Comparison Table

Clinical experts have deemed the comparator treatments presented in Table 1 to be appropriate. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. 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 1: COST COMPARISON TABLE FOR AEDs FOR THE TREATMENT OF POS IN ADULT PATIENTS WITH EPILEPSY WHO ARE NOT SATISFACTORILY CONTROLLED WITH CONVENTIONAL THERAPY

Drug/Comparator	Strength	Dosage Form	Price (\$)	Recommended Daily Dose	Daily Cost (\$)	Annual Cost (\$)
Eslicarbazepine (Aptiom)	200 mg 400 mg 600 mg 800 mg	Tablet	[REDACTED] ^a	800 to 1,200 mg once daily ^b	[REDACTED] ^a	[REDACTED]
Lacosamide (Vimpat)	50 mg 100 mg 150 mg 200 mg	Film-coated tablet	2.4900 3.5000 4.6400 5.7200	200 mg to 400 mg in 2 divided doses ^c	7.00 to 11.44	2,555 to 4,176
Perampanel (Fycompa)	2 mg 4 mg 6 mg 8 mg 10 mg 12 mg	Tablet	9.4500	4 mg to 12 mg once daily ^d	9.45	3,449

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Drug/Comparator	Strength	Dosage Form	Price (\$)	Recommended Daily Dose	Daily Cost (\$)	Annual Cost (\$)
Other AEDs of interest						
Carbamazepine (Tegretol, generics)	200 mg	Tablet	0.1540	800 mg to 1,200 mg in 2 to 4 divided doses	0.62 to 0.92	225 to 337
	100 mg	Chewtab	0.0380			
	200 mg	Chewtab	0.0749			
	200 mg	CR tablet	0.0930		0.37 to 0.56	136 to 204
	400 mg	CR tablet	0.1859			
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	EC tablet	0.0724	375 mg to 4,000 mg ^e in divided doses	0.20 to 2.08	74 to 760
	250 mg		0.1301			
	500 mg		0.2604			
Gabapentin (Neurontin, generics)	100 mg	Capsule	0.1060	900 mg to 1,800 mg in 3 divided doses	0.77 to 1.54	282 to 565
	300 mg	Capsule	0.2578			
	400 mg	Capsule	0.3072			
	600 mg	Tablet	1.3045 ^f			
Lamotrigine (Lamictal, generics)	25 mg	Tablet	0.0936	100 mg to 500 mg in 2 divided doses	0.37 to 1.85	137 to 675
	100 mg		0.3735			
	150 mg		0.5505			
Levetiracetam (generics)	250 mg	Film-coated tablet	0.8000 ^g	1,000 mg to 3,000 mg in 2 divided doses	1.95 to 5.40	712 to 1,971
	500 mg		0.9750 ^g			
	750 mg		1.3500 ^g			
Oxcarbazepine (Trileptal, generics)	150 mg	Tablet	0.6209 ^g	600 mg to 2,400 mg in 2 divided doses	2.00 to 7.28	731 to 2,658
	300 mg		0.9102 ^g			
	600 mg		1.8204 ^g			
Phenytoin sodium (Dilantin, generics)	30 mg	Capsule	0.0560	300 mg to 600 mg in 3 divided doses	0.23 to 0.47	85 to 170
	50 mg	Tablet	0.0768			
	100 mg	Capsule	0.0776			
Topiramate (Topamax, generics)	25 mg	Tablet	0.3128	200 mg to 400 mg in 2 divided doses	1.19 to 1.77	433 to 646
	100 mg		0.5929			
	200 mg		0.8854			
Valproic acid (Depakene, generics)	250 mg	Capsule	0.1366	1,000 mg to 4,000 mg in divided doses ^h	0.82 to 3.30	301 to 1,204
	500 mg	Enteric caplet	0.4125			
Vigabatrin (Sabril)	500 mg	Tablet	0.9110	2,000 mg to 3,000 mg in 2 divided doses	3.64 to 5.47	1,330 to 1,995
	0.5 g	Sachet	0.91			

AED = antiepileptic drug; chewtab = chewable tablet; CR = controlled release; ER = extended release; POS = partial-onset seizure.

^a Manufacturer's confidential submitted price; 1,200 mg dose assumes the splitting of 800 mg tablets (i.e., 1.5 tablets) as per product monograph.

^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.¹

^c Initial dose is 50 mg twice daily, increasing by 50 mg twice daily each week until maintenance dose is reached, based on response and tolerability.⁹

^d Initial dose is 2 mg daily in the absence of enzyme-inducing AEDs (e.g., carbamazepine, oxcarbazepine, phenytoin), or 4 mg daily in their presence. Dose may be increased by 2 mg daily no more frequently than at one-week intervals.¹⁰

^e Initial dose is 5 mg to 10 mg/kg/day; maximum dose is 60 mg/kg/day; doses of more than 250 mg per day should be divided. Daily dose in table based on person weighing 70 kg.

^f Manitoba formulary (January 2014).

^g Saskatchewan formulary (January 2014).

^h Initial dose is 15 mg/kg/day; maximum dose is 60 mg/kg/day. Dose in table based on person weighing 70 kg.

Note: All prices from Ontario Drug Benefit Formulary (January 2014) unless otherwise indicated.

APPENDIX 2: REVIEWER WORKSHEETS

Summary of Manufacturer's Submission

TABLE 4: MANUFACTURER'S CALCULATED DOSE-WEIGHTED AVERAGE COST PER DAY OF LACOSAMIDE AND PERAMPANEL

Drug Product	Eslicarbazepine acetate (Aptiom)
Treatment	ESL 800 mg or 1,200 mg + AED
Comparator(s)	Lacosamide + AED or perampanel + AED
Study Question	What is the daily cost of ESL relative to perampanel or lacosamide when used as adjunctive therapy to concomitant AEDs for the treatment of adults with refractory partial-onset epileptic seizures who are not satisfactorily controlled on conventional therapy?
Type of Economic Evaluation	Cost-minimization analysis
Target Population	Adults with refractory partial-onset epileptic seizures who are not satisfactorily controlled with conventional therapy
Perspective	Canadian public payer
Outcome(s) Considered	Drug costs
Key Data Sources	
Cost	ODB formulary, manufacturer's confidential price, IMS PharmaStat Ontario 2014 public-utilization data for comparators (dose-weighted average cost), mean trial dose for ESL (dose-weighted average cost)
Clinical Efficacy	NMA of placebo-controlled studies
Harms	NMA of placebo-controlled studies
Time Horizon	One day (daily drug cost)
Results for Base Case	Including an 8% markup, the dose-weighted average daily drug cost of ESL (██████) is less expensive than that of lacosamide (\$7.6202) and perampanel (\$10.2060)

AED = antiepileptic drug; ESL = eslicarbazepine acetate; NMA = network meta-analysis; ODB = Ontario Drug Benefit.

Manufacturer's Results

The manufacturer calculated dose-weighted average costs per day for lacosamide and perampanel using Ontario public data for January to May 2014 (Table 5). The dose-weighted average cost per day for ESL was derived using the average daily dose of ESL in two trials of 883 mg to estimate the percentage of patients who would use the 1,200 mg rather than the 800 mg dose (Table 6).

TABLE 5: MANUFACTURER’S CALCULATED DOSE-WEIGHTED AVERAGE COST PER DAY OF LACOSAMIDE AND PERAMPANEL

Comparator	List Price per Unit (\$)	Total Units Reimbursed January to May 2014	Weighted Average Cost per Unit (\$)	Weighted Average Cost per Day (\$)	Weighted Average Cost per Day With Markup ^a (\$)
Lacosamide					
50 mg	2.4900	232,240	3.53	7.06	7.62
100 mg	3.5000	97,922			
150 mg	4.6400	46,448			
200 mg	5.7200	87,638			
TOTAL		464,248			
Perampanel					
2 mg	9.4500	2,433	9.45	9.45	10.21
4 mg		662			
6 mg		966			
8 mg		1,056			
10 mg		0			
12 mg		0			
TOTAL		5,117			

Data: Ontario Drug Benefit (ODB) Formulary list prices (November 2014), IMS PharmaStat Ontario public-utilization data, January to May 2014.

^a ODB markup of 8% applied.

Source: Adapted from manufacturer’s submitted economic report, Table 11.

TABLE 6: MANUFACTURER’S CALCULATED DOSE-WEIGHTED AVERAGE DAILY MAINTENANCE COST OF ESLICARBAZEPINE ACETATE

Daily Dose Eslicarbazepine Acetate	Cost per Day (\$)	Utilization by Dose	Weighted Average Cost per Day (\$)	Weighted Average Cost per Day With Markup ^a (\$)
800 mg	██████	79.3%	██████	██████
1,200 mg	██████	20.7%	██████	██████

^a Ontario Drug Benefit markup of 8% applied.

Note: Data: Manufacturer’s confidential price; average dose of 883 mg from clinical trials.^{7,8} Assumes 1,200 mg dose is given as 1.5 800 mg tablets.

Source: Adapted from manufacturer’s submitted economic report, Table 12.

CADTH Common Drug Review Results

The CADTH Common Drug Review (CDR) was able to duplicate the manufacturer’s results using Ontario public data from IMS Health, with only trivial differences in the number of lacosamide units reimbursed in January through May of 2014. Updating the analysis to include utilization data from January to September 2014 had a negligible effect on dose-weighted costs; the lacosamide market share per dose was nearly identical and, while there were some market share per-dose changes for perampanel between May and September due to the 10 mg and 12 mg doses starting to be reimbursed, the flat pricing across doses rendered those changes moot. CDR ran a sensitivity analysis using utilization from all the Canadian public plans available in the IMS Health database from January to May 2014, which resulted in a dose-weighted average daily cost for lacosamide of \$7.30 per day (\$7.89 with an 8% markup) using Ontario Drug Benefit Formulary list prices, with the average daily cost of perampanel again remaining at \$9.45 (\$10.21 with markup). CDR used the manufacturer’s utilization estimates in all subsequent analyses.

When extrapolated to a full year, the dose-weighted average cost of ESL excluding markup is [REDACTED] less expensive than that of lacosamide and [REDACTED] less expensive than that of perampanel per patient.

TABLE 7: RELATIVE ANNUAL COSTS OF ESLICARBAZEPINE COMPARED WITH LACOSAMIDE AND PERAMPANEL

Comparator	Dose-Weighted Average Daily Cost ^a (\$)	Dose-Weighted Average Annual Cost ^a (\$)	Relative Annual Cost Compared With ESL ^a (\$)
Eslicarbazepine acetate	[REDACTED]	[REDACTED]	Reference
Lacosamide	7.62	3,004	[REDACTED]
Perampanel	10.21	4,023	[REDACTED]

^a Ontario Drug Benefit markup of 8% applied.

While the manufacturer’s use of the mean ESL dose from the clinical trials to estimate the proportion of patients taking the 800 mg and 1,200 mg of ESL appears reasonable in the absence of real-world utilization data, there is uncertainty that these proportions will apply in clinical practice. CDR ran sensitivity analyses varying the proportion of patients taking 1,200 mg daily from 0% to 100%; ESL remains a cost savings in all estimations (save the highly unlikely case of 100% of patients taking the 1,200 mg dose), although the amount of savings expected varies considerably (Table 8).

TABLE 8: SAVINGS EXPECTED AT VARYING ESLICARBAZEPINE MAINTENANCE DOSE—UTILIZATION RATES

Proportion of Patients Taking 1,200 mg ESL Daily	Dose-Weighted Average Cost Per Day Without Markup (\$)	Dose-Weighted Average Cost Per Day With Markup (\$) ^a	Daily Cost Relative to Average Lacosamide (\$) ^b	Daily Cost Relative to Average Perampanel (\$) ^b
0%	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
20%	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
20.7% (manufacturer’s assumption)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
40%	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
60%	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
80%	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
100%	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

ESL = eslicarbazepine acetate; ODB = Ontario Drug Benefit.

^a ODB markup of 8% applied.

^b Dose-weighted average daily cost of \$7.62 for lacosamide and \$10.21 for perampanel, including markup.

TABLE 9: KEY LIMITATIONS

Identified Limitation	Description	Implication
Clinical similarity between comparators uncertain	The assumption of clinical similarity between ESL and lacosamide or perampanel is based on an indirect comparison with limitations (see CDR Clinical Review Report, Appendix 7). This increases uncertainty in the assumption of clinical similarity underlying the CMA.	Increased uncertainty in the assumption that ESL is clinically similar to perampanel and lacosamide.
Appropriate comparators omitted	The manufacturer considered only lacosamide and perampanel as potential comparators to ESL in the submitted analysis and excluded other AEDs used as adjunctive therapy, including lamotrigine, topiramate, gabapentin, and levetiracetam, all of which are less expensive than ESL. The relative safety and efficacy of ESL versus these other adjunctive AEDs is unknown.	ESL will likely result in cost savings compared with the current list prices of lacosamide and perampanel, but is more expensive than many other AEDs used as adjunctive therapy for refractory POS.
Uncertainty in proportion of patients who will use 1,200 mg ESL daily	The manufacturer used the mean ESL dose from the extension studies of trials 301 and 302 to estimate that 20.7% of patients might use the more expensive 1,200 mg dose in clinical practice. This approach appears reasonable; however, due to uncertainty inherent in the estimation, CDR explored the costs associated with 0%, 20%, 40%, 60%, 80%, and 100% of patients using 1,200mg daily.	Some uncertainty in the extent of cost savings relative to lacosamide and perampanel, although even at 100% of patients using the 1,200 mg dose (██████ daily, including 8% markup), the daily cost of ESL would ████████ more expensive than the dose-weighted average cost of lacosamide (\$7.63; ODB list price plus 8% markup)
Titration schedules and one-day time horizon	In its calculations, the manufacturer did not account for titration schedules of AED initiation due to the one-day time horizon. Additionally, the one-day time horizon makes it more difficult to conceptualize cost differences per patient-year.	Likely minimal. ESL and perampanel have flat-rate pricing for most doses, and all three comparators have similar and relatively short titration schedules though exact timing may vary significantly according to individual response and tolerance. Estimates on one-year cost differences per patient have been provided by CDR.

AED = antiepileptic drug; CDR = CADTH Common Drug Review; CMA = cost-minimization analysis; ESL = eslicarbazepine acetate; ODB = Ontario Drug Benefit; POS = partial-onset seizure.

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