Common Drug Review
Pharmacoeconomic Review Report

February 2017

Drug	Brivaracetam (Brivlera)
Indication	Adjunctive therapy in the management of partial-onset seizures (POS) in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy
Reimbursement Request	As per indication and in a similar manner as lacosamide, perampanel, and eslicarbazepine
Dosage Form(s)	10 mg, 25 mg, 50 mg, 75 mg, and 100 mg oral tablets
NOC Date	March 9, 2016
Manufacturer	UCB Canada Inc.

Brivaracetam (Brivlera) Common Drug Review Pharmacoeconomic Report was prepared using PharmaStat data from QuintilesIMS. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health and not those of QuintilesIMS.

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 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.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update – Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

AED	antiepileptic drug
CDR	CADTH Common Drug Review
NMA	network meta-analysis
ODB	Ontario Drug Benefit
POS	partial-onset seizures

SUMMARY

Background

Brivaracetam (Brivlera) is indicated as adjunctive therapy in the management of partial-onset seizures (POS) in adult patients (≥ 18 years) with epilepsy who are not satisfactorily controlled with conventional therapy.[1] Brivaracetam is available in 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg tablets at a market price of $4.32 for all strengths. The recommended starting dose of brivaracetam is 50 mg twice daily, with the dose adjusted to between 25 mg and 100 mg twice daily, depending on response. The daily cost of brivaracetam is $8.64. The manufacturer is requesting reimbursement in line with the Health Canada indication, with similar criteria to that of lacosamide, perampanel, and eslicarbazepine.

Summary of the Economic Analysis Submitted by the Manufacturer

The manufacturer submitted a cost-minimization analysis[2] comparing brivaracetam with lacosamide, perampanel, and eslicarbazepine when used as adjunctive therapy to concomitant antiepileptic drugs (AEDs) in the management of POS in adult patients who are not satisfactorily controlled with conventional therapy. The perspective was that of a Canadian public drug plan with a time horizon of one year. The assumption of "broad similarity" was based on the results of an unpublished network meta-analysis (NMA). Costs for lacosamide, perampanel, and eslicarbazepine were derived using Ontario Drug Benefit (ODB) Formulary list prices. Costs for brivaracetam were derived using the current market price of $4.32 per tablet. All costs included an 8% markup with an $8.83 dispensing fee applied every 30 days, and were dose-weighted using a uniform distribution across the recommended maintenance dose ranges in the respective product monographs.

The manufacturer concluded that, at $3,513 per patient, the dose-weighted average annual cost of brivaracetam was $275 less than that of lacosamide ($3,788 per patient, based on a minor mathematical correction by the CADTH Common Drug Review [CDR]), $319 less than that of perampanel ($3,833 per patient), and $363 less than that of eslicarbazepine ($3,876 per patient).

Key Limitations

Uncertainty in the Assumption of Clinical Similarity

There are no head-to-head trials comparing brivaracetam with active comparators in patients with POS inadequately controlled with conventional AEDs. In the submitted NMA, no significant differences in efficacy, all-cause discontinuation, discontinuation due to treatment-emergent adverse events serious adverse events, dizziness, fatigue, or somnolence were found between brivaracetam and lacosamide, perampanel, retigabine/ezogabine (not approved in Canada), and eslicarbazepine; however, brivaracetam had a statistically significantly increased risk of nausea compared with perampanel and a reduced risk of nausea compared with eslicarbazepine. The wide credible intervals associated with the NMA estimates for brivaracetam versus the other treatments increase uncertainty in the manufacturer's assumption of similarity across drugs, as statistically non-significant differences do not necessarily imply treatment equivalence or non-inferiority. Of note, a published indirect treatment comparison[3] of brivaracetam and levetiracetam showed no statistical differences with respect to efficacy and adverse events.

Appropriate Comparators Omitted

The manufacturer compared brivaracetam with lacosamide, perampanel, and eslicarbazepine, but did not include any other drugs used in Canada as adjunctive therapy in refractory POS (e.g., lamotrigine, topiramate, gabapentin). While many of these drugs have broader indications and/or reimbursement

criteria and, therefore, may have been used earlier in therapy, they are all less expensive than brivaracetam, and their safety, tolerability, and efficacy relative to brivaracetam are unknown (Table 1). Of particular interest is levetiracetam, a less expensive drug ($536 to $1,294 per patient per year, depending on dose) in the same class as brivaracetam. A published indirect treatment comparison found few significant differences in efficacy between the two drugs.[3]

Dose-Distribution Assumption Unlikely

The manufacturer assumed a uniform dose distribution across the monograph–recommended maintenance doses for all comparators, omitting the lowest-strength tablet available for each comparator. A uniform dose distribution is unlikely and may have overestimated the average annual cost of lacosamide (the only comparator with graduated pricing, i.e., price of higher-strength tablets is greater than that of lower strengths), resulting in overestimation of the savings associated with brivaracetam. As well, lower doses of brivaracetam, particularly the 25 mg strength, are likely to replace at least some of the utilization of lower strengths of its comparators (Table 11). Utilization data from QuintilesIMS retrieved by CDR indicate that 35% of perampanel claims, 37% eslicarbazepine claims, and 31% of lacosamide claims reimbursed by the ODB Program in the first quarter of 2016 were for strengths excluded in the manufacturer's analysis, supporting the necessity of considering lower strengths in the cost calculations. Additionally, the utilization data indicate considerable use of lower-strength tablets to achieve daily doses could be achieved in a more cost-efficient manner through the use of higher strengths (e.g., two lacosamide 50 mg tablets administered twice daily rather than one 100 mg tablet administered twice daily). Therefore, omission of lower-strength tablets in the manufacturer's analysis is likely to result in underestimation of the average daily costs across all comparators, with the effect most pronounced for flat-priced comparators such as brivaracetam. In the absence of sufficient utilization data for brivaracetam, it is difficult to estimate what the real-world average daily cost of therapy will be for this drug in relation to its comparators.

Issues for Consideration

Publicly Available List Prices May Not Reflect Actual Costs to Public Plans

The actual costs paid by Canadian public drug plans for perampanel, lacosamide, and eslicarbazepine are likely lower than those listed on publicly available formularies, which reduce the relative attractiveness of the submitted price of brivaracetam. See Appendix 1 for price-reduction analyses exploring this possibility.

Combination Therapy with Perampanel, Lacosamide, or Eslicarbazepine

The clinical expert consulted by CDR noted that, in some situations, physicians may consider combining brivaracetam with perampanel, lacosamide, or eslicarbazepine rather than substituting one for another. These combinations would be more costly than several other combinations of AEDs, particularly those consisting of older AEDs.

Pediatric Use

Like lacosamide,[4] perampanel,[5] and eslicarbazepine,[6] brivaracetam is not indicated for pediatric patients.[1] However, according to the clinical expert consulted by CDR, lacosamide is frequently used in children and adolescents with refractory POS; perampanel is beginning to be used for this population, and it is likely that eslicarbazepine will be as well. Thus, it is also likely that brivaracetam will be used in pediatric patients as clinicians gain familiarity with it.

Impending Patent Expiry

The patents for lacosamide (Vimpat) are due to expire in early 2017,[7] with market exclusivity ending in September 2018,[8,9] which may lead to the availability of less expensive generic versions, making the relative cost of brivaracetam at the submitted price less attractive thereafter.

Results and Conclusions

CDR performed a reanalysis to address the identified limitations associated with the dose distribution of lacosamide, and to remove dispensing fees and markups from the calculations. At the currently marketed price of $4.32 per tablet, and using the manufacturer's dosing assumptions, the average annual cost of brivaracetam ($3,154 per patient) was less than that of lacosamide ($3,408 per patient), perampanel ($3,449 per patient), and eslicarbazepine ($3,489) at 2016 ODB Formulary list prices; however, due to cost-inefficient dispensing patterns, there is considerable uncertainty in the relative costs for all four comparators in the real-world setting. Brivaracetam is considerably more expensive than levetiracetam ($397 to $1,098), and a published indirect treatment comparison found no significant differences in efficacy between these drugs. Brivaracetam is more expensive than most other comparators used for patients with refractory POS. The combination of brivaracetam with perampanel, lacosamide, or eslicarbazepine would be more costly than other combinations of AEDs.

Cost Comparison Table

The clinical expert consulted by CDR deemed the comparator treatments presented in Table 1 to be appropriate. 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 PARTIAL-ONSET SEIZURES 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 ($)
Brivaracetam (Brivlera)	**10 mg 25 mg 50 mg 75 mg 100 mg**	**Tablet**	**4.3200[a]**	**25 to 100 mg twice daily[a]**	**8.64**	**3,154**
Eslicarbazepine (Aptiom)	200 mg 400 mg 600 mg 800 mg	Tablet	9.5600	800 to 1,200 mg once daily[b]	9.56 to 14.34[b]	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 to 400 mg in 2 divided doses[c]	7.00 to 11.60	2,555 to 4,234

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	9.4500	4 to 12 mg once daily[d]	9.45	3,449
Other AEDs of interest						
Carbamazepine (Tegretol, generics)	200 mg 100 mg 200 mg 200 mg 400 mg	Tablet Chewable tablet Chewable tablet CR tablet CR tablet	0.1540 0.0380 0.0749 0.0930 0.1859	800 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 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 to 4,000 mg[e] in divided doses	0.52 to 2.08	190 to 760
Gabapentin (generics)	100 mg 300 mg 400 mg 600 mg 800 mg	Capsule Capsule Capsule Tablet Tablet	0.0749 0.1821 0.2171 0.3256[f] 0.4341[f]	900 to 1,800 mg in 3 divided doses	0.77 to 1.54	282 to 565
Lamotrigine (Lamictal, generics)	25 mg 100 mg 150 mg	Tablet	0.0936 0.3735 0.5505	100 to 500 mg in 2 divided doses	0.37 to 1.85	137 to 675
Levetiracetam (generics)	250 mg 500 mg 750 mg	Film-coated tablet	0.4459 0.5432 0.7523	1,000 to 3,000 mg in 2 divided doses	1.09 to 3.01	397 to 1,098
Oxcarbazepine (Trileptal, generics)	150 mg 300 mg 600 mg	Tablet Tablet Tablet	0.6209[f] 1.2414[f] 1.8750[f]	600 to 2,400 mg in 2 divided doses	2.48 to 7.50	906 to 2,738
Phenytoin sodium (Dilantin, generics)	30 mg 50 mg 100 mg	Capsule Tablet Capsule	0.0861 0.0871 0.1344	300 to 600 mg in 3 divided doses	0.40 to 0.81	147 to 294

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 to 400 mg in 2 divided doses	1.19 to 1.77	433 to 646
Valproic acid (Depakene, generics)	250 mg 500 mg	Capsule Enteric caplet	0.1366 0.4125	1,000 to 4,000 mg in divided doses[e]	0.82 to 3.30	301 to 1,204
Vigabatrin (Sabril)	500 mg 0.5 g	Tablet Sachet	0.9110 0.9110[f]	2,000 to 3,000 mg in 2 divided doses	3.64 to 5.47	1,330 to 1,995

AED = antiepileptic drug; CR = controlled release; EC = enteric coated.
All prices from ODB Formulary (July 2016), unless otherwise indicated.
[a] Manufacturer's submitted price. Initial dose is 50 mg twice daily which, based on response, may be adjusted to between 25 mg and 100 mg twice daily.[1]
[b] Initial dose is 400 mg daily, increasing to 800 mg after one to two weeks. Dose may be increased to 1,200 mg daily, if required, after at least one week on the 800 mg dose.[6] While the product monograph specifies that the 1,200 mg dose should be taken as one and one-half 800 mg tablets, it is possible that some patients will receive it as two 600 mg tablets at a daily, cost of $19.12.
[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.[4]
[d] Initial dose is 2 mg daily in the absence of enzyme-inducing AEDs (e.g., carbamazepine, oxcarbazepine, phenytoin), or 4 mg in their presence. Dose may be increased by 2 mg daily no more frequently than at one week intervals.[5]
[e] Initial dose is 15 mg/kg/day; maximum dose is 60 mg/kg/day. Doses greater than 250 mg/day should be divided. Daily dose in table based on body weight of 70 kg.[10,11]
[f] Saskatchewan formulary (July 2016).

APPENDIX 1: PRICE-REDUCTION ANALYSIS

To assess the impact of potential price variability across jurisdictions, the likelihood that publicly listed formulary prices are different from actual costs to public plans, and the possible availability of generic versions of some comparators within the next several years, CDR conducted analyses exploring the relative savings or additional cost of brivaracetam compared with lacosamide, perampanel, and eslicarbazepine in various price-reduction scenarios. These analyses are based on an assumption of uniform proportional use of doses for each comparator within the recommended dose ranges, and cost-efficient dispensing (i.e., dispensing of strengths to achieve the lowest possible daily cost for a given daily dose). This may not be reflective of real-world utilization and costs given evidence from utilization data of cost-inefficient dispensing as well as the low likelihood of uniform proportional dosing. For example, average daily costs for lacosamide under differing weighting methods to account for cost-inefficient dispensing range from $7.96 (Table 10) to $9.86 (Table 11) per patient per day, while $8.64 represents the lowest average daily cost possible for brivaracetam.

TABLE 2: ADDITIONAL COST (SAVINGS) PER YEAR WITH BRIVARACETAM VERSUS LACOSAMIDE AT VARIOUS PRICE-REDUCTION SCENARIOS

		Brivaracetam Average Annual Drug Cost (Cost Savings)				
		Submitted Price: $8.64	**10% Reduction: $7.78**	**25% Reduction: $6.48**	**50% Reduction: $4.32**	**75% Reduction: $2.16**
Lacosamide (Uniform Dose-Weighted Average Annual Drug Cost)	**At list price: $9.37**	($255.50)	($570.86)	($1,043.90)	($1,832.30)	($2,620.70)
	10% reduction: $8.41	$85.41	($229.95)	($702.99)	($1,491.39)	($2,279.79)
	25% reduction: $7.01	$596.78	$281.42	($191.63)	($980.03)	($1,768.43)
	50% reduction: $4.67	$1,449.05	$1,133.69	$660.65	($127.75)	($916.15)
	75% reduction: $2.34	$2,301.33	$1,985.97	$1,512.93	$724.53	($63.87)

Source: Uniform dose-weighted average cost based on ODB Formulary list price for lacosamide, and manufacturer's submitted price for brivaracetam.

As shown in Table 2, the submitted daily cost of brivaracetam is less than the uniform dose-weighted average annual cost of lacosamide at ODB list prices, but brivaracetam would be more costly if the cost of lacosamide is reduced by 10% (threshold at 8%).

TABLE 3: ADDITIONAL COST (SAVINGS) PER YEAR WITH BRIVARACETAM VERSUS PERAMPANEL AT VARIOUS PRICE-REDUCTION SCENARIOS

		Brivaracetam Average Annual Drug Cost (Cost Savings)				
		Submitted Price: $8.64	10% Reduction: $7.78	25% Reduction: $6.48	50% Reduction: $4.32	75% Reduction: $2.16
Perampanel (Average Annual Drug Cost)	**At list price: $9.45**	($295.65)	($611.01)	($1,084.05)	($1,872.45)	($2,660.85)
	10% reduction: $8.51	$49.28	($266.08)	($739.12)	($1,527.53)	($2,315.93)
	25% reduction: $7.09	$566.66	$251.30	($221.74)	($1,010.14)	($1,798.54)
	50% reduction: $4.73	$1,428.98	$1,113.62	$640.58	($147.83)	($936.23)
	75% reduction: $2.36	$2,291.29	$1,975.93	$1,502.89	$714.49	($73.91)

Source: Average cost based on ODB Formulary list price for perampanel, and manufacturer's submitted price for brivaracetam.

As shown in Table 3, at the submitted price, brivaracetam is no longer a cost saving compared with perampanel when the cost of perampanel is reduced by 10% (threshold at 9%).

TABLE 4: ADDITIONAL COST (SAVINGS) PER YEAR WITH BRIVARACETAM VERSUS ESLICARBAZEPINE AT VARIOUS PRICE-REDUCTION SCENARIOS

		Brivaracetam Average Annual Drug Cost (Cost Savings)				
		Submitted Price: $8.64	10% Reduction: $7.78	25% Reduction: $6.48	50% Reduction: $4.32	75% Reduction: $2.16
Eslicarbazepine (Average Annual Drug Cost)	**At list price: $9.56**	($335.80)	($651.16)	($1,124.20)	($1,912.60)	($2,701.00)
	10% reduction: $8.60	$13.14	($302.22)	($775.26)	($1,563.66)	($2,352.06)
	25% reduction: $7.17	$536.55	$221.19	($251.85)	($1,040.25)	($1,828.65)
	50% reduction: $4.78	$1,408.90	$1,093.54	$620.50	($167.90)	($956.30)
	75% reduction: $2.39	$2,281.25	$1,965.89	$1,492.85	$704.45	($83.95)

Source: Average cost based on ODB Formulary list price used to estimate eslicarbazepine cost and manufacturer's submitted price for brivaracetam.

As shown in Table 4, at the submitted price, brivaracetam is no longer a cost saving compared with eslicarbazepine when the cost of eslicarbazepine is reduced by 10% (threshold at 10%).

APPENDIX 2: REVIEWER WORKSHEETS

TABLE 5: SUMMARY OF MANUFACTURER'S SUBMISSION

Drug Product	Brivaracetam (Brivlera)
Treatment	Brivaracetam 25 mg to 100 mg twice daily
Comparator(s)	Lacosamide 100 mg to 200 mg twice daily Perampanel 4 mg to 12 mg once daily Eslicarbazepine 400 mg to 800 mg once daily
Study Question	What is the cost of brivaracetam relative to alternative-branded AED drugs such as lacosamide, perampanel, and eslicarbazepine?
Type of Economic Evaluation	Cost comparison
Target Population	As per the indication: as adjunctive therapy in the management of partial-onset seizures in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy
Perspective	Canadian public payer
Outcome(s) Considered	Drug costs
Key Data Sources	
Cost	Manufacturer's submitted and current market price for brivaracetam ODB Formulary list prices for comparators ODB dispensing fees and markups included
Clinical Efficacy	Unpublished network meta-analysis[12]
Harms	Unpublished network meta-analysis[12]
Time Horizon	1 year
Results for Base Case	At ODB list prices, the annual cost of brivaracetam ($3,513.32 per patient) was $274.63[a] less than that of lacosamide ($3,787.95[a] per patient), $319.30 less than perampanel ($3,832.62 per patient), and $362.66 less than eslicarbazepine ($3,875.98 per patient) when an 8% markup and dispensing fees of $8.83 were included every 30 days

AED = antiepileptic drug; ODB = Ontario Drug Benefit.
[a] Values corrected from $310.44 and $3,823.76 respectively, due to an error in the dispensing fee calculation for the 300 mg daily dose of lacosamide.

Manufacturer's Results

The manufacturer submitted a cost-minimization analysis comparing brivaracetam (Brivlera) 25 mg to 100 mg twice daily with the Ontario Drug Benefit (ODB) list prices of lacosamide (Vimpat) 100 mg to 200 mg twice daily, perampanel (Fycompa) 4 mg to 12 mg once daily, and eslicarbazepine (Aptiom) 400 mg to 800 mg daily. An ODB markup of 8% and an $8.83 dispensing fee were applied every 30 days. The manufacturer assumed a uniform patient distribution across recommended maintenance doses of all comparators (i.e., excluding the lowest available dose for each comparator) and used unspecified "QuintilesIMS Rx Dynamics data on uptake in Ontario" to estimate the current market share of the comparators (Table 6).

Note that the following results have been corrected by CDR due to an error in the manufacturer's calculation of the dispensing fee for the 300 mg dose of lacosamide.

TABLE 6: MANUFACTURER'S ESTIMATED WEIGHTED AVERAGE COST OF BRIVARACETAM VERSUS COMPARATORS

Treatment	Unit Dose (mg)	Unit Cost ($)[a]	Daily Dosage (mg)	Cost per Day ($) (Includes Markup and Dispensing Fee)[a]	Patient Distribution[b]	Weighted Average Cost per Day ($)	Weighted Average Cost per 365 Days ($)	Estimated Market Share of Comparators[c]
Brivaracetam	10	$4.32	20.0	$9.63	0.0%	$0.00		
	25	$4.32	50.0	$9.63	25.0%	$2.41		
	50	$4.32	100.0	$9.63	25.0%	$2.41		
	75	$4.32	150.0	$9.63	25.0%	$2.41		
	100	$4.32	200.0	$9.63	25.0%	$2.41		
	Weighted total for brivaracetam					**$9.63**	**$3,513.32**	**NA**
Lacosamide	50	$2.53	100.0	$5.75	0.0%	$0.00		
	100	$3.50	200.0	$7.85	33.3%	$2.62		
	150	$4.71	300.0	$10.46[d]	33.3%	$3.49[d]		
	200	$5.80	400.0	$12.82	33.3%	$4.27		
	Weighted total for lacosamide					**$10.38[d]**	**$3,787.95[d]**	[redacted]
Perampanel	2	$9.45	2.0	$10.50	0.0%	$0.00		
	4	$9.45	4.0	$10.50	20.0%	$2.10		
	6	$9.45	6.0	$10.50	20.0%	$2.10		
	8	$9.45	8.0	$10.50	20.0%	$2.10		
	10	$9.45	10.0	$10.50	20.0%	$2.10		
	12	$9.45	12.0	$10.50	20.0%	$2.10		
	Weighted total for perampanel					**$10.50**	**$3,832.62**	[redacted]
Eslicarbazepine	200	$9.56	200.0	$10.62	0.0%	$0.00		
	400	$9.56	400.0	$10.62	33.3%	$3.54		
	600	$9.56	600.0	$10.62	33.3%	$3.54		
	800	$9.56	800.0	$10.62	33.3%	$3.54		
	Weighted total for eslicarbazepine					**$10.62**	**$3,875.98**	[redacted]

Adapted from Table 4 of the manufacturer's economic submission.[2]

[a] Comparator unit prices are ODB list prices, accessed February 2016. Unit cost for brivaracetam provided by manufacturer. Markup of 8% and $8.83 dispensing fee were applied every 30 days.

[b] Manufacturer assumed equal distribution across recommended maintenance doses.

[c] Reported by manufacturer as based on "QuintilesIMS Rx Dynamics data on uptake in Ontario."

[d] Originally reported by manufacturer as $10.75 cost per day, $3.58 weighted average cost per day, $10.48 weighted total cost per day, and $3,823.76 weighted average cost per year due to an error in the dispensing fee calculation for the 300 mg daily dose of lacosamide.

The manufacturer then reported the incremental cost associated with the weighted average annual cost of brivaracetam versus each comparator, as well as a weighted average "blended" incremental cost, where the annual comparator costs were combined using the manufacturer's estimate of their current market share (see Table 7). The estimated annual cost of brivaracetam ($3,513 per patient) was $275 less than that of lacosamide ($3,788 per patient), $319 less than that of perampanel ($3,833 per patient), $363 less than that of eslicarbazepine ($3,876 per patient), and [redacted] less than that of the blended basket of comparators.

TABLE 7: MANUFACTURER'S TOTAL AND INCREMENTAL COSTS OF BRIVARACETAM VERSUS COMPARATORS

Comparator	Daily Cost	Annual Cost	Incremental Cost Brivaracetam Versus Comparator	
			Per Day	Per 365 Days
Brivaracetam	$9.63	$3,513.32	-	-
Lacosamide	$10.38[a]	$3,787.95[a]	–$0.75[a]	**–$274.63[a]**
Perampanel	$10.50	$3,832.62	–$0.87	**–$319.30**
Eslicarbazepine	$10.62	$3,875.98	–$0.99	**–$362.66**
Weighted average "blended" incremental costs[b]			[redacted]	[redacted][a]

Adapted from Table 6 of manufacturer's economic submission.[2]
[a] Originally reported as $10.48 daily cost, $3,823.76 annual cost, –$0.85 daily incremental, and –$310.44 annual incremental cost of brivaracetam, and –$[redacted] weighted average blended incremental cost due to an error in the dispensing fee calculation for the 300 mg daily dose of lacosamide.
[b] Weighted average blended incremental costs are derived using the market shares specified (Table 6).

The manufacturer also conducted a series of sensitivity analyses to test the robustness of their base-case analysis, including the inclusion of a 14-day titration for lacosamide (titration ignored for other comparators due to flat pricing), and using the World Health Organization defined daily dose as well as the total average dose derived using real-world utilization data from "QuintilesIMS ODB database" February 2015 through January 2016, instead of the manufacturer's assumed uniform distribution. Due to flat-rate pricing across doses for all other included comparators, these sensitivity analyses affected only the estimated cost of lacosamide and the weighted average blended costs. The incremental savings of brivaracetam versus lacosamide ranged from $238 to $304 per patient per year, depending on the sensitivity analysis (Table 8).

TABLE 8: MANUFACTURER'S TOTAL AND INCREMENTAL COSTS OF BRIVARACETAM VERSUS COMPARATORS IN SENSITIVITY ANALYSES

Sensitivity Analysis	Daily Cost of Lacosamide	Annual Cost of Lacosamide	Incremental Cost of Brivaracetam Versus Lacosamide	Incremental Cost of Brivaracetam Versus Blended Costs
Base case	$10.38	$3,787.95	–$274.63	[redacted]
Inclusion of lacosamide titration	$10.38[a]	$3,751.41[a]	–$238.09[a]	[redacted][a]
WHO DDD (300 mg lacosamide)	$10.46[b]	$3,816.85[b]	–$303.53[b]	[redacted][b]
Average daily dose ([redacted] mg lacosamide applied as [redacted] mg)[c]	[redacted][b]	[redacted][b]	[redacted][b]	[redacted][b]

DDD = defined daily dose; ODB = Ontario Drug Benefit; WHO = World Health Organization.
Adapted from Table 7 of manufacturer's economic submission.[2]
[a] Originally reported by manufacturer as $10.48 daily cost, $3,785.85 annual cost, –$272.53 annual incremental cost versus lacosamide, and [redacted] annual incremental cost versus blended costs due to an error in the dispensing fee calculation for the 300 mg daily dose of lacosamide.
[b] Originally reported by manufacturer as $10.75 daily cost, $3,924.29 annual cost, –$410.97 annual incremental cost versus lacosamide, and [redacted] annual incremental cost versus blended costs due to an error in the dispensing fee calculation for the 300 mg daily dose of lacosamide.
[c] Source cited by manufacturer as "QuintilesIMS (referred to elsewhere as Rx Dynamics) ODB database," February 2015 to January 2016.

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CDR did not consider the manufacturer's weighted average "blended" incremental costs to be valid:

- Eslicarbazepine was only recently introduced onto public formularies in Canada; thus, its market share is likely still growing. Data retrieved by CDR using QuintilesIMS indicated that the Ontario public market share for eslicarbazepine relative to lacosamide and perampanel was between 1.8% and 2.5% in the first quarter of 2016, depending on the method of calculation; this is at least [redacted] times the [redacted] share estimated by the manufacturer based on QuintilesIMS Rx Dynamics data from February 2015 through January 2016.
- Comparing the cost of brivaracetam to a blended average of multiple comparators weighted by market share, even if the market share is accurate and stable, assumes that brivaracetam will displace these comparators in that same ratio. Given the differences in reported adverse-event profiles, regulatory warnings, and the suitability of each comparator for patients with differing treatment histories (e.g., patients on carbamazepine would be less likely to have eslicarbazepine added, while patients on levetiracetam would be less likely to have brivaracetam added), this seems unlikely.

CDR reviewers noted the manufacturer's assumption of a dispensing fee every 30 days may be an overestimation, as some patients would be older than 65 years of age, and thus would qualify to receive up to 100 days of medication at a time. However, the impact of this assumption is unlikely to be large, given the relatively young age of patients with epilepsy, the likelihood of dose adjustments, and the absence of the main comparators on the ODB list of chronic medications (which limits the number of dispensing fees for included medications to five annually).[13] CDR removed dispensing fees and markups (given the variability between jurisdictions) from further analyses.

Using the manufacturer's assumed dose distribution, but removing markups and dispensing fees, yields a dose-weighted average annual cost of $3,154 per patient for brivaracetam, which is $254 less than that of lacosamide ($3,408 per patient), $296 less than that of perampanel ($3,449 per patient), and $336 less than that of eslicarbazepine ($3,489 per patient) (Table 9).

TABLE 9: CDR'S ESTIMATED WEIGHTED AVERAGE COST OF BRIVARACETAM VERSUS COMPARATORS USING MANUFACTURER'S DOSE DISTRIBUTION (DISPENSING FEES AND MARKUP REMOVED)

Treatment	Unit Dose (mg)	Unit Cost[a]	Daily Dosage (mg)	Cost per Day[a]	Patient Distribution[b]	Weighted Average Cost per Day	Weighted Average Cost per 365 Days	Incremental Cost of Brivaracetam
Brivaracetam	10	$4.32	20.0	$8.64	0.0%	$0.00		
	25	$4.32	50.0	$8.64	25.0%	$2.16		
	50	$4.32	100.0	$8.64	25.0%	$2.16		
	75	$4.32	150.0	$8.64	25.0%	$2.16		
	100	$4.32	200.0	$8.64	25.0%	$2.16		
	Weighted total for brivaracetam					**$8.64**	**$3,153.60**	**Reference**
Lacosamide	50	$2.53	100.0	$5.05	0.0%	$0.00		
	100	$3.50	200.0	$7.00	33.3%	$2.33		
	150	$4.71	300.0	$9.41	33.3%	$3.14		
	200	$5.80	400.0	$11.60	33.3%	$3.87		
	Weighted total for lacosamide					**$9.34**	**$3,407.88**	**–$254.28**

Treatment	Unit Dose (mg)	Unit Cost[a]	Daily Dosage (mg)	Cost per Day[a]	Patient Distribution[b]	Weighted Average Cost per Day	Weighted Average Cost per 365 Days	Incremental Cost of Brivaracetam
Perampanel	2	$9.45	2.0	$9.45	0.0%	$0.00		
	4	$9.45	4.0	$9.45	20.0%	$1.89		
	6	$9.45	6.0	$9.45	20.0%	$1.89		
	8	$9.45	8.0	$9.45	20.0%	$1.89		
	10	$9.45	10.0	$9.45	20.0%	$1.89		
	12	$9.45	12.0	$9.45	20.0%	$1.89		
	Weighted total for perampanel					**$9.45**	**$3,449.25**	**–$295.65**
Eslicarbazepine	200	$9.56	200.0	$9.56	0.0%	$0.00		
	400	$9.56	400.0	$9.56	33.3%	$3.19		
	600	$9.56	600.0	$9.56	33.3%	$3.19		
	800	$9.56	800.0	$9.56	33.3%	$3.19		
	Weighted total for eslicarbazepine					**$9.56**	**$3,489.40**	**–$335.80**

CDR = CADTH Common Drug Review.
[a] Comparator unit prices are ODB list prices, accessed July 2016. Unit cost for brivaracetam provided by manufacturer.
[b] Manufacturer assumed equal distribution across recommended maintenance doses.

The manufacturer's base-case analysis uses a uniform dose distribution across product monograph–recommended maintenance doses; however, this is not supported by data. Additionally, by only including the higher doses, incremental cost calculations are biased in favour of flat-rate priced comparators relative to those with graduated pricing. In reality, the lower doses of flat-rate priced comparators can be expected to replace at least some of the lower-dose and lower-cost utilization of lacosamide and, thus, these costs should have been considered. In fact, 35% of perampanel claims and 37% of eslicarbazepine claims reimbursed by Ontario in the first quarter of 2016 were for the lowest strengths (2 mg and 200 mg tablets respectively), while 31% of claims were for 50 mg lacosamide tablets, supporting the necessity of considering lower doses in cost calculations. These percentages remain similar when calculated by the proportion of individual patients on each strength within each month of Ontario public claims data (January, February, and March 2016). CDR conducted a reanalysis using QuintilesIMS public claims data for January through March 2016 to estimate the proportion of patients using each daily dose of lacosamide, and assuming cost-efficient dispensing. Under these assumptions, the annual cost of brivaracetam ($3,154 per patient) is $248 more than that of lacosamide ($2,905 per patient) (Table 10).

TABLE 10: CDR'S REANALYSIS OF INCREMENTAL COST OF BRIVARACETAM RELATIVE TO LACOSAMIDE BASED ON UTILIZATION-BASED DOSE DISTRIBUTION FOR LACOSAMIDE

Treatment	Unit Dose (mg)	Unit Cost[a]	Daily Dosage (mg)	Cost per Day ($)[a]	Patient Distribution[b]	Weighted Average Cost per Day	Weighted Average Cost per 365 Days	Incremental Cost of Brivaracetam
Brivaracetam	10	$4.32	20.0	$8.64	20.0%	$1.73		
	25	$4.32	50.0	$8.64	20.0%	$1.73		
	50	$4.32	100.0	$8.64	20.0%	$1.73		
	75	$4.32	150.0	$8.64	20.0%	$1.73		
	100	$4.32	200.0	$8.64	20.0%	$1.73		
	Weighted total for brivaracetam					**$8.64**	**$3,153.60**	**Reference**

Treatment	Unit Dose (mg)	Unit Cost[a]	Daily Dosage (mg)	Cost per Day ($)[a]	Patient Distribution[b]	Weighted Average Cost per Day	Weighted Average Cost per 365 Days	Incremental Cost of Brivaracetam
Lacosamide	50	$2.53	100.0	$5.75	31.1%	$1.57		
	100	$3.50	200.0	$7.85	28.0%	$1.96		
	150	$4.71	300.0	$10.46	14.4%	$1.35		
	200	$5.80	400.0	$12.82	26.5%	$3.08		
	Weighted total for lacosamide					**$7.96**	**$2,905.36**	**$248.24**

CDR = CADTH Common Drug Review; ODB = Ontario Drug Benefit.
[a] Lacosamide unit prices are the ODB list prices, accessed July 2016. Unit cost for Brivlera provided by manufacturer.
[b] Lacosamide dose distribution is based on QuintilesIMS public claims data from January to March 2016. Brivaracetam distribution is assumed and unlikely to reflect clinical practice, however it does not impact the weighted average or incremental costs given its flat-rate pricing.

Interestingly, the manufacturer also did not consider the 1,200 mg dose when calculating the average annual cost of eslicarbazepine, a dose included in the recommended range of the product monograph[6] and estimated to be used by 20.7% of patients in the base case of the CDR review of Aptiom.[14] Using this dose-distribution estimate, and assuming that patients taking 1,200 mg are using one and one-half 800 mg tablets, the weighted average annual cost of eslicarbazepine increases to $3,851 per patient, yielding an incremental savings with brivaracetam compared with eslicarbazepine of $697 per patient per year.

The high number of claims for lower strengths appears at least partially driven by cost-inefficient dispensing (i.e., use of multiple low-strength tablets to achieve a daily dose that could be achieved in a less costly manner by using higher strengths). For all three comparators where utilization data are available, the lowest strengths are used twice as often per day as would be expected if dispensing patterns were perfectly cost-efficient. An exploratory analysis of the potential ramifications of this can be found in Table 11, using QuintilesIMS public plan data from January 2016; the use of February or March 2016 data yields similar results.

TABLE 11: CDR'S EXPLORATORY ANALYSIS ON THE COST IMPACT OF THE USE OF MULTIPLE LOW-DOSE TABLETS TO ACHIEVE TARGET DOSING

Treatment	Unit Dose (mg)	Units Claimed January 2016	Days Supply Claimed January 2016	Units/Day	Proportion Unique Patients	Weighted Cost per Day
Lacosamide (twice daily)	50	64,966	16,544	3.93	32.5%	$3.22
	100	32,756	13,798	2.37	25.8%	$2.15
	150	15,764	7,920	1.99	14.8%	$1.38
	200	29,311	14,733	1.99	26.9%	$3.10
	Weighted total for lacosamide					**$9.86**
Perampanel (once daily)	2	4,319	1,837	2.35	33.5%	$7.45
	4	1,009	785	1.29	15.6%	$1.90
	6	1,137	1,107	1.03	17.3%	$1.68
	8	1,202	1,216	0.99	19.1%	$1.78
	10	457	457	1.00	6.9%	$0.66
	12	458	458	1.00	7.5%	$0.71
	Weighted total for perampanel					**$14.18**

Treatment	Unit Dose (mg)	Units Claimed January 2016	Days Supply Claimed January 2016	Units/Day	Proportion Unique Patients	Weighted Cost per Day
Eslicarbazepine (once daily)	200	876	373	2.35	42.1%	$9.45
	400	314	211	1.49	21.1%	$3.00
	600	240	150	1.60	10.5%	$1.61
	800	323	309	1.05	26.3%	$2.63
	Weighted total for eslicarbazepine					**$16.69**

Source: Based on January 2016 Ontario public plan data from QuintilesIMS. Unit costs can be found in Table 9.

While inefficient from a cost perspective, the apparent overuse of some strengths may be related to the recommendations for initiating therapy within individual product monographs. The lacosamide monograph[4] recommends an initial dose of 50 mg twice daily, increasing by 50 mg twice daily every week up to 200 mg twice daily depending on individual efficacy and tolerability; the average use of 3.93 units/day rather than 2 per day for the 50 mg strength may reflect continued use of this strength into the maintenance phase when dispensing 100 mg tablets would have been more cost-efficient. Similarly, the initial dose of perampanel is 4 mg daily, increasing in 2 mg increments based on response and tolerance, leading to increased use of both the 2 mg and 4 mg tablets (2.35 and 1.29 tablets per day respectively, rather than 1 per day). Eslicarbazepine is more complicated, given that the recommended starting dose is 400 mg daily, increasing up to 800 mg based on response and tolerance, with a maximum recommended dose of 1,200 mg per day for some patients.[6] While the monograph suggests the 1,200 mg daily dose be dispensed as one and one-half 800 mg tablets, it is likely that some patients are receiving two 600 mg tablets daily as a maintenance dose, increasing the use of that tablet strength, along with use of the 200 mg and 400 mg strengths.

Of note, the cost-inefficient use of lower-strength tablets disproportionately increases the weighted average daily costs of flat-priced comparators relative to lacosamide (weighted average cost of $9.86 per patient per day versus $14.18 and $16.69 for perampanel and eslicarbazepine, respectively). There were insufficient utilization data available at the time of this review to perform a similar analysis based on brivaracetam utilization. However, given that the initial dose recommended in the monograph is 50 mg twice daily, adjusted to 25 mg to 100 mg twice daily based on response and tolerability,[1] it is likely that the 25 mg and 50 mg strengths of brivaracetam will be inefficiently utilized from a cost perspective to a similar extent as the lower strengths of its comparators, which would increase the incremental cost of brivaracetam relative to lacosamide.

In short, depending on the method of analysis, the daily cost of lacosamide ranged from $7.96 to $9.86 per patient, while the submitted and lowest possible daily cost of brivaracetam was $8.64 per patient. The real-world daily cost of brivaracetam is likely to be higher than this due to cost-inefficient dispensing patterns observed for its comparators.

The patents for lacosamide (Vimpat) are due to expire in early 2017, which may lead to the availability of less expensive generic versions in the near future,[7] although lacosamide's inclusion on the Register for Innovative Drugs in effect grants the manufacturer of Vimpat market exclusivity until September 2018.[8,9] CDR conducted analyses to explore the incremental cost of brivaracetam versus its comparators under various price-reduction scenarios in Appendix 1.

A published indirect treatment comparison of levetiracetam with brivaracetam, analogues with similar mechanisms of action, found few statistically significant differences between these drugs in patients

with refractory focal seizures (refractory POS).[3] Although similar to the results of the manufacturer's NMA, these findings are not necessarily indicative of clinical equivalence or non-inferiority. Due to the need for a varying number of tablets per day to achieve levetiracetam doses within the range recommended in the product monograph (1,000 mg to 3,000 mg in two divided doses), it is not possible to accurately estimate a dose-weighted, daily-average cost using QuintilesIMS data by tablet strength, as was done for lacosamide, perampanel, and eslicarbazepine. The annual cost of levetiracetam ranges from $397 to $1,098 per patient.

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