



COMMON DRUG REVIEW

CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

BRIVARACETAM

(Brivlera — UCB Canada Inc.)

Indication: Partial-Onset Seizures in Patients with Epilepsy

Recommendation:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that brivaracetam be reimbursed for adjunctive therapy in the management of partial-onset seizures (POS) in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy, if the following clinical criteria and conditions are met:

Clinical criteria:

- Patients are currently receiving two or more antiepileptic drugs (AEDs).
- Patients are not receiving concurrent therapy with levetiracetam.
- Patients are those for whom less costly AEDs are ineffective or not clinically appropriate.

Conditions:

- Patients are under the care of a physician experienced in the treatment of epilepsy.
- The daily cost of treatment with brivaracetam should not exceed the daily cost of alternative adjunctive therapies.

Reasons for the Recommendation:

1. In four randomized controlled trials (RCTs) (Study 1252 [N = 399], Study 1253 [N = 400], Study 1254 [N = 480], and Study 1358 [N = 768]) of 12 to 16 weeks of treatment duration, treatment with brivaracetam 50 mg/day to 200 mg/day generally demonstrated statistically significantly greater reductions in POS frequency from baseline compared with placebo in patients 16 years and older with uncontrolled POS, despite concomitant treatment with 1 to 3 AEDs. Further, a greater proportion of patients taking brivaracetam achieved a 50% reduction in seizures compared with placebo.
2. In a subgroup of patients with concomitant levetiracetam use at baseline in Studies 1252, 1253, and 1254, [REDACTED].
[REDACTED]. Conversely, in patients without concomitant levetiracetam use at baseline, [REDACTED].
[REDACTED].

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3. At the submitted price of \$4.32 per tablet, the CADTH Common Drug Review (CDR) estimated that the average annual cost of brivaracetam (\$3,154 per patient) is less than that of lacosamide (\$3,408 per patient), perampanel (\$3,449 per patient), and eslicarbazepine (\$3,489), but exceeds the annual cost of other AEDs used adjunctively to treat POS.

Of Note:

1. In a manufacturer-submitted network meta-analysis (NMA), brivaracetam showed no statistically significant differences in efficacy; serious adverse events; discontinuation due to any reason; discontinuation due to adverse events; or experiencing dizziness, fatigue, and somnolence versus lacosamide, perampanel, and eslicarbazepine. However, several limitations of the NMA restrict the strength of the conclusions that may be made regarding the comparative efficacy and safety of brivaracetam.
2. CDEC noted that — as pre-specified in the CDR systematic review of brivaracetam — several older and less costly AEDs are appropriate comparators for adjunctive therapy in the management of POS in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy, in addition to lacosamide, perampanel, and eslicarbazepine. These include (but are not limited to) levetiracetam, lamotrigine, gabapentin, and clobazam.
3. CDEC noted that the use of brivaracetam in combination with eslicarbazepine, perampanel, or lacosamide has not been studied, and that the combination of brivaracetam with any of these drugs would be more costly than other combinations of AEDs.

Background:

Brivaracetam is indicated as adjunctive therapy in the management of POS in adult patients who are not satisfactorily controlled with conventional therapy. The product monograph recommends a starting dose of 50 mg twice daily (100 mg per day). Based on individual patient response and tolerability, the dose may be adjusted between 25 mg twice daily (50 mg per day) and 100 mg twice daily (200 mg per day). Brivaracetam is available as 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg tablets; 10 mg/mL oral solution; and 10 mg/mL injection. The focus of this CDR review was on the oral tablets only.

Summary of CDEC Considerations:

CDEC considered the following information prepared by CDR: a systematic review of RCTs of brivaracetam, a critique of the manufacturer's pharmacoeconomic evaluation, and a summary of information submitted by patient groups about outcomes and issues important to individuals living with POS.

Patient Input Information

No patient input was specifically received for brivaracetam. The following is a summary of key information adapted from patient input received for the CDR review of perampanel (Fycompa), as it was viewed as relevant. Two patient groups provided information in response to the CDR call for patient input of perampanel:

- POS can affect almost every aspect of a person's day-to-day life, including developmental delays, comorbidities, loss of independence, the ability to seek or maintain employment, and the ability to operate a motor vehicle safely and maintain a driver's licence. Patients with uncontrolled seizures are often placed in dangerous situations, for example, should a seizure occur while riding a bus, shopping, or crossing a street. Not knowing when a seizure might occur can result in persistent anxiety or other mood disorders. Societal attitudes have

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a significant impact on persons with epilepsy; people with the condition often face stigma, discrimination, and social isolation.

- Current drug therapies are limited by adverse effects, including cognitive and behavioural disturbances, fatigue, mood swings, depression, suicidal thoughts, and exhaustion.
- Current drug therapies are not effective for all patients and some patients continue to have uncontrolled epilepsy despite treatment. Expectations of patient groups for a new AED are that seizure frequency will be reduced, quality of life will be improved, there will be fewer adverse effects, and the drug will be affordable and accessible.

Clinical Trials

The CDR systematic review included four multi-centre, double-blind, parallel-group, placebo-controlled, phase 3 RCTs. Study 1252 (N = 399), Study 1253 (N = 400), Study 1254 (N = 480), and Study 1358 (N = 768) enrolled patients with uncontrolled POS, with or without secondary generalized seizures, despite receiving 1 to 3 AEDs. Patients with cluster seizures, Type IA non-motor seizures, or status epilepticus were excluded. In Studies 1252, 1253, and 1358, patients were randomized to brivaracetam 5 mg/day to 200 mg/day or matched placebo; however, only results for the Health Canada–approved doses of brivaracetam 50 mg/day to 200 mg/day were reported in the CDR review. Study 1254 was a flexible-dose study in which patients initially randomized to brivaracetam 20 mg/day or matched placebo, were up-titrated to 50 mg/day, 100 mg/day, or 200 mg/day during a dose-finding period. The duration of the double-blind treatment was 12 weeks in all trials with the exception of Study 1254 which had a 16-week treatment period (i.e., combined 8-week dose-finding and 8-week maintenance periods).

Key limitations of the available evidence are the lack of active-comparator trials with other clinically relevant comparator AEDs (e.g., perampanel, lacosamide, eslicarbazepine, and older AEDs used as adjunct therapy), the lack of validation and minimal clinically important differences (MCIDs) in patients with epilepsy for the measured outcomes, the lack of up-titration in the fixed-dose trials, and the short duration of the treatment for an intervention intended for chronic use.

Outcomes

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

- Seizures measured as:
 - proportion of seizure-free patients (100% seizure reduction of all seizure types)
 - reduction in partial-onset seizure frequency per week or per 28-days (Study 1358 only) from baseline to the end of treatment, which was the primary efficacy end point in all the trials
 - proportion of patients with a 50% or greater reduction in seizure frequency.
- Patient-reported outcomes:
 - Quality of Life in Epilepsy Inventory Form 31 (QOLIE-31-P) — a measure of seizure worry, daily activities and social functioning, energy and fatigue, emotional well-being, cognitive functioning, medication effects, health status, and overall quality of life during the treatment period.
 - EuroQoL 5-Dimensions (EQ-5D) Visual Analogue Scale (VAS) — a generic quality of life instrument in which respondents rate their own health, based on a VAS with anchors of worst and best imaginable health states.

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- Global Impression of Change using a Patient Global Evaluation Scale (P-GES) or Clinician Global Evaluation Scale (C-GES) completed at the end of treatment by patients and investigators, respectively, who evaluated treatment from the start of the trial.

Efficacy

- The proportion of patients who were seizure-free was statistically significantly higher in the brivaracetam groups compared with placebo, only in Study 1358:
 - Study 1358: 5.2% ($P = 0.003$) for 100 mg/day and 4.0% ($P = 0.019$) for 200 mg/day
- Seizure frequency per week (or per 28-days in Study 1358) was statistically significantly lower in the brivaracetam groups compared with placebo, with the exception of the comparison of brivaracetam 50 mg/day with placebo in Study 1252 and the combined brivaracetam doses with placebo in Study 1254, which were not statistically different. Median differences in the per cent reduction in partial-onset seizure frequency for brivaracetam compared with placebo were reported as:
 - Study 1252: -19.35% ($P = 0.004$) for 100 mg/day
 - Study 1253: -15.69% ($P = 0.003$) for 50 mg/day
 - Study 1358: -15.8% ($P < 0.001$) for 100 mg/day and -18.1% ($P < 0.001$) for 200 mg/day.
 - An MCID has been reported to be a 20% reduction in partial-onset seizure frequency over placebo; therefore, the magnitude of the reduction with brivaracetam over placebo suggests that a clinically important reduction was not achieved.
- Median differences in the per cent reduction in partial-onset seizure frequency by the stratification factor of concomitant levetiracetam use were investigated in Studies 1252, 1253, and 1254. In patients with concomitant levetiracetam use at study entry, none of the comparisons between brivaracetam and placebo were statistically significant; whereas, in patients with no concomitant levetiracetam use at study entry, all comparisons between brivaracetam and placebo were statistically significantly different.
- A statistically significantly greater proportion of brivaracetam-treated patients achieved a 50% reduction in POS compared with placebo-treated patients, with the exception of the comparison of brivaracetam 50 mg/day with placebo in Study 1252. The odds ratios of achieving a 50% reduction in seizure frequency (brivaracetam versus placebo) were reported as:
 - Study 1252: 2.13 (95% CI, 1.11 to 4.10) ($P = 0.023$) for 100 mg/day
 - Study 1253: 2.51 (95% CI, 1.27 to 4.96) ($P = 0.008$) for 50 mg/day
 - Study 1254: 2.18 (95% CI, 1.24 to 3.81) ($P = 0.006$) for combined brivaracetam doses
 - Study 1358: 2.39 (95% CI, 1.6 to 3.6) ($P < 0.001$) for 100 mg/day and 2.19 (95% CI, 1.5 to 3.3) ($P < 0.001$) for 200 mg/day
 - An MCID has been reported to be a 15% difference in the proportion of patients with a 50% responder rate compared with placebo; therefore, the difference between brivaracetam and placebo suggests the results are clinically meaningful.
- Descriptive statistics for the QOLIE-31-P and EQ-5D VAS [REDACTED]
- Overall, results for the P-GES and I-GES found that [REDACTED]

- The manufacturer conducted a Bayesian NMA to compare brivaracetam with lacosamide, perampanel, and eslicarbazepine, and retigabine (not available in Canada). The NMA suggested that there were no statistically significant differences in efficacy between brivaracetam and other adjunct AEDs. However, these results do not allow for a conclusion of equivalence or non-inferiority across drugs. Several limitations with the NMA were identified: lack of subgroup analyses on the population in the indication for brivaracetam (i.e., those ≥ 18 years old), as well as the choice of comparators (i.e., incorporation of AEDs not approved for use in Canada, and exclusion of comparators used as adjunctive therapy for refractory patients in Canadian clinical practice).
- A published indirect comparison of brivaracetam versus levetiracetam was identified by CDR. The analysis indicated that there are no statistically significant differences in efficacy between the two drugs at all dose levels. However, many of the compared doses for both brivaracetam and levetiracetam are not approved by Health Canada, the included studies had different numbers of previous AEDs at baseline, and some of the brivaracetam studies had patients receiving concomitant levetiracetam.

Harms (Safety and Tolerability)

- The proportion of patients with at least one serious adverse event (SAE) ranged from 2.0% to 5.3% among the brivaracetam groups compared with 0% to 7.4% among the placebo groups. The most common SAE was convulsion in both the brivaracetam (1.0% to 1.9% of patients) and placebo (0.8% to 3.0% of patients) groups. There was one death in the placebo groups and four deaths in the brivaracetam groups, of which only one death due to brain hypoxia was considered to be possibly related to brivaracetam.
- The proportion of patients who withdrew due to adverse events (WDAEs) ranged from 5.0% to 8.3% among the brivaracetam groups compared with 2.0% to 5.0% among the placebo groups. The most common reason for a WDAE was convulsion in both the brivaracetam (0.4% to 2.0% of patients) and placebo (0.4% to 1.0% of patients) groups.
- The proportion of patients who experienced at least one treatment-emergent adverse event ranged from 63% to 75% of patients in the brivaracetam groups compared with 53% to 65% of patients in the placebo groups. Somnolence occurred more frequently with brivaracetam (6.1% to 19.4% of patients) compared with placebo (4.1% to 7.7% of patients). Other adverse events that occurred more frequently with brivaracetam compared with placebo were dizziness and fatigue. Headache was also a common adverse event and was reported in a similar proportion of brivaracetam- and placebo-treated patients.
- The duration of the treatment phases of the trials (12 to 16 weeks) are not sufficient to characterize the long-term safety of brivaracetam
- The manufacturer-submitted NMA suggested [REDACTED]

[REDACTED] As mentioned, several limitations of the NMA preclude drawing concrete conclusions as to the comparative safety of brivaracetam.

- In the published indirect comparison of brivaracetam versus levetiracetam identified by CDR, the proportion of patients experiencing adverse events was similar between treatments, except levetiracetam may be associated with a lower probability of dizziness compared with brivaracetam at high doses. The potential limitations with this analysis were previously mentioned.

Cost and Cost-Effectiveness

The manufacturer submitted the market price of \$4.32 for all strengths of brivaracetam (10 mg, 25 mg, 50 mg, 75 mg, and 100 mg tablets), for a daily cost of \$8.64 regardless of dose.

A cost-minimization analysis was provided by the manufacturer comparing brivaracetam with lacosamide, perampanel, and eslicarbazepine when used as adjunctive therapy for 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. The efficacy and safety of brivaracetam and the assessed comparators were assumed to be similar based on the results of a manufacturer-sponsored NMA. Costs for lacosamide, perampanel, and eslicarbazepine were derived using Ontario Drug Benefit (ODB) Formulary list prices. All costs included an 8% markup with an \$8.83 dispensing fee applied every 30 days. A uniform distribution of daily doses across the recommended maintenance dose ranges was assumed for brivaracetam and its comparators; this assumption only affected the estimated annual cost of lacosamide, which unlike the other drugs, does not have a flat pricing structure across strengths.

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), \$319 less than that of perampanel (\$3,833 per patient), and \$363 less than that of eslicarbazepine (\$3,876 per patient).

Key limitations in the manufacturer's analysis included: uncertainty regarding the assumption of clinical similarity; the omission of less expensive adjunctive therapies for refractory POS such as levetiracetam; the low likelihood that there is uniform utilization of doses in clinical practice; and the omission of lower doses for some comparators, which biased results in favour of flat priced comparators.

CDR performed a re-analysis to remove dispensing fees and markups from the calculations. Re-analyses were also performed based on revised dose distributions obtained from utilization data, although there were difficulties in comparing utilization data across comparators due to evidence of cost-inefficient dispensing patterns (i.e., the use of lower strength tablets to achieve daily doses that could be achieved in a more cost efficient manner through the use of higher strengths). At \$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. Due to cost-inefficient dispensing patterns, there is considerable uncertainty regarding the relative real-world costs of brivaracetam and the assessed comparators.

Brivaracetam is considerably more expensive than levetiracetam (annual cost \$397 to \$1,098), and a published indirect treatment comparison found no significant differences in efficacy between these drugs. Brivaracetam is also more expensive than most other comparators used as adjunctive therapy for patients with refractory POS.

CDEC Members:

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

Regrets:

September 21, 2016: Four CDEC members were absent.

January 18, 2017: None

Conflicts of Interest:

None

About This Document:

CDEC provides formulary reimbursement recommendations or advice to CDR participating drug plans. CDR clinical and pharmaco-economic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

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