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CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

LEVETIRACETAM (PDP-LEVETIRACETAM — PENDOPHARM, A DIVISION OF PHARMASCIENCE INC.)

Indication: Epilepsy

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that levetiracetam oral solution (100 mg/mL) should be reimbursed as adjunctive therapy for the management of patients with epilepsy only if the following conditions are met.

Conditions for Reimbursement
Initiation criteria
1. Levetiracetam oral solution should be reimbursed in a manner similar to other reimbursed levetiracetam formulations.

Pricing conditions
1. The drug plan cost of levetiracetam oral solution should not exceed the drug plan cost of treatment with the least costly levetiracetam formulation reimbursed for the treatment of epilepsy.

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Reasons for the Recommendation

1. Seven clinical trials were included in the CADTH review of levetiracetam oral solution. Six of these trials were conducted with a reference product of levetiracetam tablets (studies N051, N132, N138, N0159, N166, and N1057) and one trial was conducted with a reference oral solution (Study N1009) that is not the oral solution under review. In studies N051, N132, N138, N0159, and N1057, adjunctive treatment with levetiracetam tablets was associated with a significantly greater reduction in seizure frequency compared with placebo in adult (16 years to 70 years) and pediatric (four years to 16 years) patients with partial onset and generalized tonic-clonic seizures who were refractory to previous treatments. In Study N166, the response rate was significantly greater with levetiracetam tablets than placebo in patients with refractory myoclonic seizures and in children with juvenile myoclonic epilepsy (JME). Study N1009, which included patients aged one month to less than four years, demonstrated that a significantly greater proportion of patients treated with levetiracetam oral solution achieved a 50% or greater reduction in the frequency of partial onset seizures from baseline compared to patients treated with placebo.
2. Levetiracetam oral solution was evaluated through Health Canada's Submissions Relying on Third-Party Data pathway, so no evidence using the specific formulation of levetiracetam under review (100 mg/mL) was available. However, bioequivalence was demonstrated between the tablet and oral solution formulations of the reference product in an in vivo study and between [redacted] the oral solution currently under review in an in vitro study.
3. Based on a cost comparison, levetiracetam oral solution ($2,972 per patient per year) would increase costs to the drug plans by an additional $2,339 to $2,686 annually compared with currently reimbursed formulations of levetiracetam at the submitted price.

Implementation Considerations

- For the drug plans requiring reassessment for eligibility of reimbursement, renewal of levetiracetam oral solution should be determined in a manner similar to other levetiracetam formulations.
- If the pricing condition above cannot be achieved, levetiracetam oral solution will likely lead to increased annual costs to the drug plans. To manage this, public payers should consider reimbursing levetiracetam oral solution only for patients unable to swallow levetiracetam tablets.

Discussion Points

- Comparative data of levetiracetam oral solution to other antiepileptic drugs available in liquid formulation were not available for this review. Comparative data between pdp-levETIRAcetam oral solution and [redacted] is limited to an in vitro comparison of the physicochemical properties of the drugs.

- CDEC acknowledged that, in the absence of a commercially available levetiracetam oral solution, some patients who could not swallow tablets (such as children younger than six years of age) were being treated with a compounded formulation.
- CDEC acknowledged that there is potential for levetiracetam oral solution to be prescribed beyond the approved Health Canada indication as adjunctive treatment. The clinical expert indicated that, in clinical practice, levetiracetam may be considered as a first-line treatment option for epilepsy.
- Levetiracetam is known to be associated with behavioural and psychiatric adverse reactions, which are more common in children than adults. The benefit-risk profile of levetiracetam should be carefully considered for patients who may be more susceptible to these adverse effects, such as children with autism.

Background

Levetiracetam is a drug of the pyrrolidine class. The mechanism of action of levetiracetam is not known. Levetiracetam oral solution (100 mg/mL) is approved by Health Canada for the following indications:

- For adults: as adjunctive therapy in the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy.
- For pediatrics: as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalization in adolescents, children, and infants (from one month of age) with epilepsy; myoclonic seizures in adolescents from 12 years of age with JME; and primary generalized tonic-clonic seizures in adolescents from 12 years of age with idiopathic generalized epilepsy.

In adults (older than 18 years) and adolescents (12 years to 17 years) weighing 50 kg or more, treatment with levetiracetam oral solution (100 mg/mL) should be initiated at a dose of 1,000 mg/day given as 500 mg twice daily. Depending on the clinical response and tolerability, the daily dose may be increased every two weeks by increments of 1,000 mg to a maximum recommended daily dose of 3,000 mg. The recommended dose for levetiracetam oral solution differs according to age and weight in pediatric patients. As per the product monograph, levetiracetam oral solution is the preferred formulation over tablets for use in infants and children younger than six years or weighing less than 25 kg and in any patients unable to swallow tablets.

Summary of Evidence Considered by CDEC

The committee considered the following information prepared by CADTH: a review of the beneficial and harmful effects of levetiracetam oral solution for the treatment of patients with epilepsy based on the summary of clinical evidence submitted by the sponsor and a critique of the sponsor's cost comparison. The committee also considered input from a clinical expert with experience in treating patients with epilepsy and from the Goodman Pediatric Formulations Centre (GPFC).

Summary of Patient Input

There was no patient input received for this review. One organization, the GPFC (which is not a patient group or association), submitted a letter of support for levetiracetam oral solution. The GPFC was founded in 2016 with initial funds provided by the Morris and Rosalind Goodman Family Foundation. Today, GPFC's philanthropic funding base is largely from the CHU Sainte-Justine Hospital Foundation. Pharmascience and Pendopharm are fully owned by the Goodman family.

Clinical Trials

The CADTH clinical review was based on a summary of clinical evidence provided by the sponsor in accordance with the CADTH tailored review process and was focused on the clinical studies that were referenced in the product monograph for pdp-levETIRAcetam. All evidence provided in the submission was based on third-party data using the levetiracetam tablet (with the exception of study N1009, in which the Keppra oral solution was used). The body of evidence for the review included seven trials:

- Three trials (N051 [N = 324], N132 [N = 294], and N138 [N = 286]) were conducted in adult patients 16 to 70 years of age with refractory partial onset epilepsy.
- Two trials (N159 [N = 216] and N1009 [N = 116]) were conducted in pediatric patients (aged one month to 16 years) with refractory partial onset epilepsy.

- Two trials (N166 [N = 122] and N1057 [N = 164]) were conducted in a mixed population of pediatric and adult patients (four years to 65 years of age) with refractory generalized myoclonic or tonic-clonic epilepsy.

Of the seven trials, six (N051, N132, N138, N159, N166, and N1057) were multi-centre, double-blind, parallel-group, randomized, placebo-controlled, phase III trials that investigated the efficacy and safety of the levetiracetam tablet (the reference product) given as adjunctive therapy (i.e., added on to a background regimen of one to three antiepileptic drugs) in patients aged four years to 70 years for the treatment of refractory epilepsy. Study N1009 was a randomized controlled trial that investigated the levetiracetam oral solution (reference product: Keppra oral solution,100 mg/mL) for the treatment of patients with refractory partial onset epilepsy aged one month to four years.

The trials investigated different doses of levetiracetam (1,000 mg/day to 3,000 mg/day in adults; up to 60 mg/kg per day in children). In trial N1009, the dose of levetiracetam oral solution was determined by the patient's age. Patients aged one month to less than six months initiated treatment with levetiracetam at 20 mg/kg per day on day 1 and were maintained on a dose of 40 mg/kg per day; patients aged six months to less than four years initiated treatment with levetiracetam at 25 mg/kg per day on day 1 and were maintained on a dose of 50 mg/kg per day. The duration of the double-blind evaluation period in studies N051, N132, N138, N159, N166, and N1057 ranged from 12 weeks to 24 weeks; the duration of treatment in study N1009 was five days.

The proportion of patients who discontinued from the trials was low (less than 15%) across the trials (except for study N051, in which 18.0% of patients in the levetiracetam 2,000 mg/day group were discontinued from the study, and study N1057, in which 16.7% patients in the placebo group discontinued from the study).

One bioequivalence study of the levetiracetam tablet versus the oral solution (both reference products) and one in vitro study of physicochemical test data ([redacted]) were also summarized by the sponsor.

Outcomes

Of the outcomes reported in the summary of clinical evidence submitted by the sponsor, the committee discussed the following: reduction in seizure frequency, responder rate (proportion of patients who achieved a 50% or greater reduction in seizure frequency), and harms. The primary outcome in five trials (N051, N132, N138, N159, and N1057) was the reduction in seizure frequency per week from baseline. The primary outcome in studies N1009 and N166 was the proportion patients who achieved a reduction in seizure frequency of 50% or greater at the end of the trial.

Efficacy

Adult Population (16 Years to 70 Years of Age)

Three trials (N051, N132, and N138) included in the sponsor's summary of clinical evidence demonstrated that adjunctive treatment with levetiracetam tablets at doses of 1,000 mg/day to 3,000 mg/day led to a greater decrease in seizure frequency in adults with partial onset seizures compared with placebo.

In study N051 of adult patients with refractory partial seizures, a statistically significant greater reduction in seizure frequency (primary end point) was observed at week 12 in the levetiracetam 1,000 mg/day group compared with the placebo group (least square mean between-group difference [levetiracetam minus placebo] = 16.4%; 98% confidence interval [CI], 2.7% to 28.1%; P = 0.006) and in the levetiracetam 2,000 mg/day group compared with the placebo group (mean between-group difference [levetiracetam minus placebo] = 17.7%; 98% CI, 4.1% to 29.4%; P = 0.003). The proportion of patients who achieved a 50% or greater reduction in seizure frequency (i.e., were considered responders) was 22.8%, 31.6%, and 10.4% in the levetiracetam 1,000 mg/day, levetiracetam 2,000 mg/day, and placebo groups, respectively.

In study N132 of adult patients with refractory partial seizures, a statistically significant greater reduction in seizure frequency was observed at week 18 in the levetiracetam 1,000 mg/day group compared with the placebo group (median between-group difference [levetiracetam minus placebo] = 26.1%; P < 0.001) and in the levetiracetam 3,000 mg/day group compared with the placebo group (median between-group difference [levetiracetam minus placebo] = 30.1%; P = 0.001). (Confidence intervals were not reported in the sponsor's summary of the evidence.) The proportion of patients who achieved a 50% or greater reduction in seizure frequency (i.e.,

were considered responders) was 37.1%, 39.6%, and 7.4% in the levetiracetam 1,000 mg/day, levetiracetam 3,000 mg/day, and placebo groups, respectively.

In study N138 of adult patients with refractory partial seizures, a statistically significant greater reduction in seizure frequency was observed from baseline to the end of the add-on phase in the levetiracetam 3,000 mg/day group compared with the placebo group (median between-group difference [levetiracetam minus placebo] = 22.9%; 98% CI, 14.3% to 29.4%; P < 0.001). The proportion of patients who achieved a 50% or greater reduction of seizure frequency (i.e., were considered responders) was 42.1% and 16.7% in the levetiracetam 3,000 mg/day and placebo groups, respectively.

Pediatric Population (One Month to 16 Years of Age)

In study N159 of children aged 4 years to 16 years, a statistically significant greater reduction in seizure frequency per week was observed at week 14 in the levetiracetam 60 mg/kg per day group compared with the placebo group (median between-group difference [levetiracetam minus placebo] = 26.8%; 95% CI, 14% to 37.6%; P = 0.0002). The proportion of patients who achieved a 50% or greater reduction of seizure frequency (i.e., were considered responders) was 44.6% and 19.6% in the levetiracetam 60 mg/day and placebo groups, respectively.

In study N1009 of children aged one month to less than four years, a statistically significant greater proportion of patients were considered responders (i.e., achieved 50% or greater reduction in seizure frequency) on day 5 in the levetiracetam group than in the placebo group (levetiracetam oral solution = 43.1% versus placebo = 19.6%; odds ratio [OR] = 3.11; 95% CI, 1.22 to 8.26; P = 0.013).

Mixed Population of Children and Adults (Four Years to 65 Years of Age)

In study N166 of patients 12 years to 65 years of age with refractory myoclonic seizures and children with JME, the proportion of patients who achieved 50% or greater reduction in seizure frequency (the primary end point) at 16 weeks was statistically significantly greater in the levetiracetam 3,000 mg/day group compared with the placebo group (levetiracetam 3,000 mg/day = 58.3% versus placebo = 23.3%; OR = 4.77; 95% CI, 2.12 to 10.77; P < 0.001).

In study N1057 of patients four years to 65 years of age with idiopathic generalized epilepsy experiencing refractory generalized tonic-clonic seizures, a statistically significant greater reduction in seizure frequency was observed at 24 weeks in the levetiracetam 3,000 mg/day group compared with the placebo group (least square mean between-group difference [levetiracetam 3,000 mg/day minus placebo] = 28.31%; 95% CI, 8.97% to 47.64%; P = 0.004). The proportion of patients who achieved a 50% or greater reduction in seizure frequency (i.e., were considered responders) was 68.4% and 44.0% in the levetiracetam 3,000 mg/day and placebo groups, respectively.

No efficacy data were submitted for the levetiracetam oral solution under review; however, the sponsor included information from a bioequivalence study on the tablet and oral solution formulations of levetiracetam that was developed by the sponsor of the reference product. Results of this study showed that the 90% CIs of the geometric mean ratio of the two formulations for area under the curve (AUC) from zero to infinity, AUC from zero to t, and peak concentration (C_{max}) were within the 80% to 125% range; therefore, the bioequivalence of the two formulations was established. The sponsor also included results from an in vitro comparative analysis between [redacted]. Results showed that the non-medicinal ingredients in the formulation of the product under review compared with the reference product were qualitatively and quantitatively similar in terms of [redacted]. The amount of each ingredient in the test product was within ± 10% of the amount of each excipient in the reference product.

Harms (Safety)

The summary of clinical safety summarized by the sponsor was based on the levetiracetam tablet reference product; no safety data were collected for the levetiracetam oral solution under review.

Across the seven included studies, the proportion of patients who experienced at least one treatment-emergent adverse event was approximately the same in the levetiracetam and placebo groups and was similar across the studies in adults and children. The most frequently reported treatment-emergent adverse events were somnolence, agitation, depression, nasopharyngitis, headache, fatigue,

anorexia, and dizziness. The clinical expert consulted for this review indicated that the adverse events reported in the included trials are aligned with what is expected in clinical practice.

The percentage of patients experiencing at least one serious adverse event and the most common serious adverse events were not available in the sponsor's summary of evidence for all the studies. The same was true for the data presented regarding withdrawal due to adverse events. Information pertaining to adverse events of special interest in each study was not in the sponsor's summary of the evidence. However, it was indicated that the safety profile in pediatric patients was consistent with the safety profile of levetiracetam in adults except for behavioural and psychological adverse events, anorexia, and decreased appetite, which were more common in children than in adults.

There were no deaths reported during the treatment periods of the included trials except for study N132. In study N132, two deaths were reported: one occurred during the baseline period before randomization and one occurred in a patient who had been randomized to placebo treatment.

Cost and Cost-Effectiveness

The drug acquisition cost of a 300 mL bottle (100 mg/mL) of levetiracetam oral solution is $244.26, leading to an annual cost per patient of $2,972 at a dosage of 500 mg twice daily.

The sponsor submitted a cost comparison assessing levetiracetam oral solution versus levetiracetam compounded suspension for the treatment of children and adult patients with epilepsy and seizures who meet the criteria outlined in the clinical section. The sponsor based the cost of levetiracetam compounded suspension on the 600 mL bottle (50 mg/mL, $51.97), for an annual per-patient drug cost of $623. Levetiracetam oral solution costs $2,339 more annually per patient than the compounded suspension. The cost comparison was from the drug plan perspective and only considered drug acquisition costs; provincial dispensing fees, compounding fees, and pharmacy markups were excluded.

CADTH identified the following key limitations with the sponsor's submitted cost comparison:

- The sponsor assumed that the pharmacy-compounded suspension would be produced using 500 mg tablets; however, there was variability in the formulary prices for levetiracetam tablets across jurisdictions.
- There is uncertainty regarding the bioequivalence of the 750 mg and 500 mg tablets of levetiracetam. The sponsor assumed the pharmacy-compounded suspension would only be made using 500 mg tablets, but the bioequivalence data submitted by the sponsor were based on the 750 mg levetiracetam tablets to inform efficacy and safety. Therefore, it is unclear whether the oral solution and compounded suspension produced using 500 mg tablets are of equivalent efficacy and safety and what impact these data would have on the selection of tablets in pharmacy compounding practice.
- The sponsor only considered adult/adolescent dosing in their cost comparison, but the submitted Health Canada indication also recommends levetiracetam oral solution for children and infants with partial onset, myoclonic, and primary generalized tonic-clonic seizures. The recommended daily dose ranges from 7 mg/kg to 1,500 mg twice daily leading to highly variable annual costs which were not reported in the sponsor's submission.

CADTH conducted exploratory analyses to address some of the identified limitations, including using jurisdiction-specific costs of levetiracetam tablets to calculate the cost of the compounded suspension, assuming the compounded suspension would be made with 750 mg tablets, and including children and infant dosing in the cost comparison table. Overall, the levetiracetam oral solution would be expected to cost the drug plans an additional $2,339 and $2,686 annually compared with the compounded suspension and tablets, respectively.

For levetiracetam oral solution to be considered cost-neutral compared with levetiracetam compounded suspension and tablets in terms of drug acquisition costs, price reductions of 79% and 90%, respectively, would be required.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Dr. Kerry Mansell, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

December 9, 2020

Regrets

None

Conflicts of Interest

None