



## Context

It has been estimated that 250,000 Canadians suffer from epileptic seizures.<sup>1</sup> Epilepsy carries a significant burden of illness, reflected in poorer health and psychosocial function, and greater use of health care resources.<sup>2</sup> Epilepsy is associated with a higher prevalence of disability, unemployment, and chronic comorbidities, including gastrointestinal ulcers, stroke, urinary incontinence, bowel disorders, and psychiatric disorders.<sup>1,3</sup> Individuals with more severe and frequent seizures have a higher mortality rate than the general population.<sup>1</sup>

With the expanding list of antiepileptic drugs available in Canada and the lack of comparative trials, the choice of treatment is individualized for each patient.<sup>4</sup> First-line treatment options include lamotrigine and valproic acid for generalized seizures, carbamazepine for partial seizures, and lamotrigine, valproic acid, or ethosuximide for absence seizures.<sup>4</sup> However, standard antiepileptic drugs are sometimes associated with intolerable adverse effects and drug interactions.<sup>5</sup> Furthermore, up to 30% of patients do not achieve seizure control with conventional therapies.<sup>6-8</sup>

Levetiracetam (Keppra) is a broad-spectrum antiepileptic that has been shown to be effective for a variety of seizure types in adults and children.<sup>9,10</sup> It was approved by Health Canada in 2003 and is currently indicated as adjunctive therapy for the management of adults with epilepsy who have not responded to conventional therapy.<sup>11,12</sup> Levetiracetam has a favourable safety and tolerability profile, although some cases of behavioural adverse effects (such as aggressive behaviour and suicidal ideation) have been

reported.<sup>12</sup> Levetiracetam is a good treatment option for women of child-bearing age, individuals with comorbidities, and for the elderly, as it has no known clinically significant drug interactions.<sup>12</sup> Results from an economic analysis indicated that when levetiracetam is used in combination with other antiepileptic drugs for patients who have not responded to conventional therapy, the increase in drug costs, from the Canadian Ministry of Health perspective, may be partially offset by savings arising from a reduction in seizure frequency and the need for surgery.<sup>5</sup>

Levetiracetam is costly compared with other treatment options and is not covered by all provincial drug plans.<sup>13</sup> Lower-cost generic formulations have recently become available, but there is evidence that substitution to generic levetiracetam may increase the risk of breakthrough seizures.<sup>14-16</sup> The increase in seizure frequency with generic substitution has also been observed with other antiepileptic drugs, resulting in higher health care costs.<sup>17</sup> The American Academy of Neurology has issued a position statement opposing the generic substitution of anticonvulsants without prior consent of the physician and the patient.<sup>18</sup>

Given the issues of cost and the potential loss of seizure control with generic formulations, the role of levetiracetam in the treatment of epilepsy across Canada is of interest.

## Objectives

The purpose of this report is to provide information on the use of levetiracetam in epilepsy treatment centres across Canada. The following questions will be addressed:

- What is the role of levetiracetam in the management of different types of epileptic seizures (e.g., complex partial seizures, simple partial seizures, primary tonic-clonic seizures, and absence seizures) in Canada?
- Is levetiracetam used first-, second-, or third-line as adjunctive or monotherapy?

## Findings

The findings of this Environmental Scan are not intended to provide a comprehensive review of the topic. The results of this report are based on a limited literature search and personal communications with Canadian health care officials. This report is based on information gathered as of May 6, 2011.

The reimbursement status for levetiracetam varies among provincial drug plans in Canada.<sup>13</sup> Levetiracetam is covered as a regular benefit in Alberta, Saskatchewan, Prince Edward Island, and

Quebec. Coverage is restricted to patients who have not responded to conventional antiepileptic drugs in British Columbia, New Brunswick, Nova Scotia, and Newfoundland. Levetiracetam is not covered by provincial drug plans in Ontario and Manitoba.

Information provided by Canadian health care officials who participated in the provincial scan is summarized in Table 1. No response was received from epilepsy treatment centres in Quebec and Newfoundland.

Levetiracetam is used in epileptic treatment centres across Canada for the management of partial seizures in children and adults. It is also used for generalized seizures (including tonic-clonic and myoclonic seizures) in most treatment centres, but is not always considered a treatment option for absence seizures. Levetiracetam is routinely used first-line in Alberta and Saskatchewan, where it is covered by provincial drug plans. First-line use in other provinces may be considered in special cases, such as children who have had cardiac or transplantation surgery. It is used as either monotherapy or adjunctive therapy in most treatment centres, on a case-by-case basis.

Table 1: Levetiracetam Use in Epilepsy Treatment Centres across Canada

Treatment Centre	Population	Levetiracetam Use	Formulary Status <sup>13</sup>
<b>British Columbia</b>			
Vancouver General Hospital, Epilepsy Centre, Vancouver	Adults	Levetiracetam is used for the treatment of both primary generalized seizures (including absence, myoclonic, or tonic-clonic seizures) and partial seizures with or without secondary generalization.  It is most often used as second-line monotherapy or adjunctive therapy, but can also be used in some cases as first-line monotherapy.	Coverage restricted to use as adjunctive therapy in patients who have not responded to other conventional antiepileptic drugs.

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Treatment Centre	Population	Levetiracetam Use	Formulary Status <sup>13</sup>
BC Children’s Hospital, Epilepsy Program, Vancouver	Children	For primary generalized tonic-clonic seizures, lamotrigine or valproic acid are first-line, followed by levetiracetam or topiramate. Levetiracetam is used for partial seizures with or without secondary generalization, typically after three other medications have failed, because of BC Pharmacare restrictions. For absence seizures, ethosuximide is first-line, valproic acid is second-line, lamotrigine is third-line, and levetiracetam may be considered after these options have failed. Levetiracetam is mainly used as adjuvant therapy, but if patients do well, monotherapy may be used. Levetiracetam may be used first-line in certain populations, such as children who have had cardiac surgery.	
<b>Alberta</b>			
Foothills Medical Centre, Epilepsy Clinic, Calgary	Adults	Levetiracetam is used as first-line treatment for different types of seizures, as either monotherapy or adjunctive therapy.	Covered as a regular benefit.
Stollery Children’s Hospital, Comprehensive Epilepsy Program, Edmonton	Children	Levetiracetam is used second- or third-line as adjunctive therapy for children with complex partial seizures.	
<b>Saskatchewan</b>			
Royal University Hospital, Epilepsy Program, Saskatoon	Adults and children	Levetiracetam is used as first-line treatment for different types of seizures, as either monotherapy or adjunctive therapy.	Covered as a regular benefit.
<b>Manitoba</b>			
Health Sciences Centre, Epilepsy Clinic, Winnipeg	Adults	Levetiracetam is used as adjunctive therapy for complex partial seizures, simple partial seizures, primary tonic-clonic seizures, and absence seizures. It is not typically used first- or	Not covered.

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Treatment Centre	Population	Levetiracetam Use	Formulary Status <sup>13</sup>
		second-line, because of the excessive cost and the lack of Manitoba Pharmacare approval as first-line, except when there is a medical condition, such as severe liver disease, for which levetiracetam would be a good choice. It is rarely used as monotherapy.	
Children’s Centre, Pediatric Neurology, Winnipeg	Children	Levetiracetam is used as a second- or third-line drug for both partial seizures and tonic-clonic seizures, as either adjunctive therapy or monotherapy.	
<b>Ontario</b>			
London Health Sciences Centre, Epilepsy Programme, London	Adults and children	Levetiracetam is mainly used as a second- or third-line adjuvant treatment for complex and simple partial seizures. It is also used as monotherapy and as first-line treatment in some cases. It is not used for absence seizures, and rarely for primary generalized seizures.	Not covered.
Hospital for Sick Children, Epilepsy Clinic, Toronto	Children	Levetiracetam is primarily used for complex partial seizures and primary generalized seizures. It is usually used as a second- or third-line treatment, as either adjunctive or monotherapy. There are certain groups of patients in whom levetiracetam is used first-line, such as those who are on immunosuppressants post-transplantation, because of its primarily renal metabolism and lack of drug interactions. It is rarely used for absence seizures.	
Toronto Western Hospital, Epilepsy Clinic, Toronto	Adults	Levetiracetam is used second- or third-line, as either monotherapy or adjunctive therapy for all seizure types.	

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<b>Nova Scotia*</b>			
IWK Health Centre, Neurology Department, Halifax	Children	Levetiracetam is primarily used for all types of partial seizures as a third-line agent because of the excessive cost and the lack of Nova Scotia Pharmacare approval as first-line. It is also sometimes used for generalized epilepsies (such as juvenile myoclonic epilepsy and idiopathic generalized epilepsy) as a second- or third-line drug. It is generally used as monotherapy for partial and generalized seizures, but in more refractory patients, it may be used as adjuvant therapy. Levetiracetam is not used for absence seizures.	Coverage restricted to use as adjunctive therapy in patients who have not responded to conventional treatments.
Queen Elizabeth II Health Sciences Centre, Epilepsy Program, Halifax	Adults	Levetiracetam is most commonly used to treat partial onset seizures, but is also used to treat primary generalized seizures. It is a first-line drug only for patients who have an insurance plan that covers it. It is used as monotherapy or adjunctive therapy, depending on the clinical scenario.	

\*The epilepsy treatment centres in Nova Scotia also provide care to patients in New Brunswick and Prince Edward Island.

## Conclusion

Levetiracetam is used across Canada as monotherapy or adjunctive therapy for the management of partial seizures in children and adults. It is also used for generalized seizures (including tonic-clonic and myoclonic) in most treatment centres, but is not always considered a treatment choice for absence seizures. There are variations in the reimbursement of levetiracetam by the provincial drug plans. Some neurologists may consider levetiracetam to be a first line therapy for specific populations with partial seizures and primary generalized seizures.

Complementing this Environmental Scan, CADTH prepared two Rapid Response reports in 2011 pertaining to the clinical effectiveness, cost-effectiveness, and safety of levetiracetam treatment in patients with epilepsy and guidelines for pharmacological treatments in patients with epilepsy. These summaries are available for free on the CADTH website.<sup>19,20</sup>

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