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CADTH Common Drug Review

Clinical and Economic Review Report

LEVETIRACETAM (pdp-levETIRAcetam)

Pendopharm, a Division of Pharmascience Inc.

Indication: Epilepsy

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

AE	adverse event
AED	antiepileptic drug
ANCOVA	analysis of covariance
AUC	area under the curve
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
EEG	electroencephalogram
EU	European Union
GPFC	Goodman Pediatric Formulations Centre
HRQoL	health-related quality of life
ILAE	International League Against Epilepsy
ITT	intention to treat
JME	juvenile myoclonic epilepsy
LSM	least squares mean
mITT	modified intention to treat
OR	odds ratio
PGTC	primary generalized tonic-clonic seizures
PP	per protocol
QOLIE-31-P	Quality of Life in Epilepsy Inventory-31, patients
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
TEAE	treatment-emergent adverse event
UCB	Union Chimique Belge

Executive Summary

An overview of the submission details for levetiracetam (pdp-levETIRAcetam) oral solution (100 mg/mL) is provided in Table 1.

Table 1: Submitted for Review

Item	Description
Drug product	Levetiracetam (pdp-levETIRAcetam), oral solution 100 mg/mL
Indication	**Adults:** as adjunctive therapy in the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy **Pediatrics:** as adjunctive therapy in the treatment of: • partial onset seizures with or without secondary generalization in adolescents, children, and infants from 1 month of age with epilepsy • myoclonic seizures in adolescents from 12 years of age with juvenile myoclonic epilepsy • primary generalized tonic-clonic seizures in adolescents from 12 years of age with idiopathic generalized epilepsy
Reimbursement request	For patients treated with levetiracetam who cannot take oral tablets due to swallowing difficulties
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	July 11, 2019
Sponsor	Pendopharm, a division of Pharmascience Inc.

NOC = Notice of Compliance.

Introduction

Epilepsy is a chronic neurological disorder that is defined by at least 2 unprovoked seizures occurring more than 24 hours apart, 1 unprovoked seizure and a probability of further seizures that is similar to the general recurrence risk after 2 unprovoked seizures (at least 60%, occurring over the next 10 years), or a diagnosis of an epilepsy syndrome.[1] The International League Against Epilepsy (ILAE) classifies epilepsy based on seizure type, epilepsy type, and epilepsy syndrome.[2] Seizure types are classified as generalized onset, focal (or partial) onset, or unknown onset. Epilepsy types include generalized, focal, combined generalized and focal, and unknown epilepsy.[2] Generalized seizure types include generalized tonic-clonic, myoclonic, absence, tonic, clonic, and atonic. Epilepsy is associated with an increased risk of a variety of psychiatric and medical comorbidities that can adversely impact quality of life as well as life expectancy.[3]

Approximately 0.6% of the Canadian population has epilepsy.[4] The reported incidence of epilepsy in the pediatric population ranges from 41 to 187 per 100,000; the incidence is highest in the first year of life and declines to adult levels by the end of the first decade.[5] Each day in Canada, an average of 42 people, or approximately 15,500 people annually, are diagnosed with epilepsy.[4]

Epilepsy is considered to be medically refractory epilepsy (or drug-resistant epilepsy, pharmacoresistant epilepsy, or intractable epilepsy) when a patient fails to achieve sustained seizure freedom after adequate trials of 2 tolerated antiepileptic drugs (AEDs) either as monotherapy or in combination.[6] Approximately, 20% to 40% of patients with epilepsy are likely to have refractory epilepsy.[6,7]

The goals of epilepsy treatment are to control seizures, avoid adverse events (AEs), and maintain or restore health-related quality of life (HRQoL).[8] The selection of AEDs is usually based on various factors which include the effectiveness of the drug for the patient's seizure type, potential AEs, and interactions with medications, comorbid medical conditions, age, patient preference, and cost.[8]

Levetiracetam is a drug of the pyrrolidine class. As with other drugs in this class, the mechanism of action of levetiracetam is not known.[9] Levetiracetam is a broad spectrum antiseizure medication, and has shown to be effective for control of various seizure types in both adults and children with epilepsy.[10-12] Until recently, the only oral formulation of levetiracetam approved by Health Canada was the levetiracetam tablet, which is indicated as adjunctive therapy for the management of adults with epilepsy who have not responded to conventional therapy.[10] In the absence of availability of an oral solution, levetiracetam oral suspension (50 mg/mL) has been compounded and used for patients (adult and children) who are not able to swallow levetiracetam tablets.[13,14] In the US and the European Union (EU), levetiracetam tablets[15] and oral solution[16] have been marketed for more than 10 years in the treatment of patients with refractory epilepsy in adults and for pediatric patients with partial onset seizures, myoclonic seizures, and generalized tonic-clonic seizures.[13,16]

The focus of the current CADTH review is the levetiracetam oral solution (pdp-levETIRAcetam, 100 mg/mL),[9] which was approved by Health Canada in July 2019. For adults, it is indicated as adjunctive therapy in the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy. For pediatrics, it is indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalization in adolescents; children and infants (from 1 month of age) with epilepsy; myoclonic seizures in adolescents from 12 years of age with juvenile myoclonic epilepsy (JME); and primary generalized tonic-clonic (PGTC) seizures in adolescents from 12 years of age with idiopathic generalized epilepsy.[9]

The Health Canada-recommended dose as add-on therapy in adults (> 18 years) and adolescents (12 years to 17 years) weighing 50 kg or more is as follows: treatment should be initiated at a dose of 1,000 mg/day given as twice-daily dosing (500 mg twice daily). Depending on the clinical response and tolerability, the daily dose may be increased every 2 weeks by increments of 1,000 mg to a maximum recommended daily dose of 3,000 mg (1,500 mg twice daily).[9] There are limited safety data from controlled clinical trials at doses higher than 3,000 mg/day (approximately 40 patients), therefore these doses are not recommended.[9]

Based on the Health Canada product monograph, pdp-levETIRAcetam oral solution is the preferred formulation over tablets for use in infants and children younger than 6 years or less than 25 kg, and in any patients unable to swallow tablets.[9] The recommended dose for levetiracetam oral solution differs according to age and weight in pediatric patients. For add-on therapy in infants aged 1 month to less than 6 months (Table 3), the initial therapeutic dose is 7 mg/kg twice daily.[9] Depending upon the clinical response and tolerability, the dose can be increased up to 21 mg/kg twice daily. Dose changes should not exceed increases or decreases of 7 mg/kg twice daily every 2 weeks. Infants should start treatment with pdp-levETIRAcetam 100 mg/mL oral solution.

The objective of this report is to review the beneficial and harmful effects of pdp-levETIRAcetam oral solution for the treatment of patients (children and adults) with epilepsy based on the summary of clinical evidence submitted by the sponsor, which is based on

third-party data (referencing Keppra tablets and oral solution, Union Chimique Belge [UCB]) included in the Health Canada pdp-levETIRAcetam product monograph.

Stakeholder Engagement

The information in this section is a summary of input provided by a group advocating for patients who responded to CADTH's call for patient input and from the clinical expert consulted by CADTH for the purpose of this review.

Patient Input

The Goodman Pediatric Formulations Centre (GPFC) is not a patient group or association, but has a team of clinicians who work closely with patients and has shared their views on the importance of the commercial availability of levetiracetam oral solution. The GPFC disclosed that Pharmascience and Pendopharm are fully owned by Goodman family. However, the information submitted to CADTH was written by GPFC and was not reviewed by anyone outside of the GPFC. The GPFC indicated that GPFC's positions and actions are completely independent from their industry partners.

In their submission, the GPFC provided reasons why they thought access to the commercial oral solution of levetiracetam is important for Canadian children, as follows.

Children differ from adults in many aspects that may affect pharmacotherapy, including drug disposition and toxicity, and the capabilities for drug administration. Numerous medications given to children have no commercially available, age-appropriate pharmaceutical forms, leading to many challenges including manipulation of dosage forms designed for adults by health care professionals and parents.

In Canada, oral levetiracetam is given as an off-label extemporaneous suspension given the Canadian label has no pediatric indication, and no oral solution is approved. This is in contrast with the US and the EU where the first pediatric indication for levetiracetam was granted in 2005. Furthermore, levetiracetam oral solution (100 mg/mL) and concentrate for IV infusion (500 mg/5 mL) have been on the US and EU markets for more than 10 years. This highlights how Canada has fallen behind.

Although the majority of children with epilepsy are responsive to treatment, approximately one-third will remain refractory and experience seizures despite treatment with at least 2 appropriate AEDs and frequently require polypharmacy.[17] Within the polypharmacy required to optimize seizure control in these patients, effective AEDs with favourable benefit and risk ratios such as levetiracetam are in demand.

Today, there is no justification for levetiracetam compounding given the risks it bears and knowing a safe and efficacious oral solution exists and has been used for more than a decade in children around the world.

Clinician Input

The clinical expert consulted by CADTH for this review indicated that levetiracetam is effective for a broad range of seizure types and that the levetiracetam oral solution would fill a need for young infants and children with epilepsy who are unable to swallow tablets, as well as for adults and children with swallowing difficulties.

The clinical expert considered reduction in seizure frequency to be the best way to determine a response to treatment and that a response to treatment should be assessed every 6 months. The clinical expert indicated that in clinical practice, patients would be considered to be responsive to treatment if they were seizure free for a minimum of 3 times the interseizure interval or 12 months.

The clinical expert indicated that levetiracetam oral solution could be used in community and hospital settings and that it may be prescribed by primary care physicians. Levetiracetam has been available for many years, it's place in therapy is already established, and the introduction of this formulation would not be anticipated to change the treatment landscape.

Clinical Evidence

Description of Studies

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 focused on the clinical studies that are referenced in the product monograph for pdp-levETIRAcetam. All the evidence provided in the submission is based on third-party data using the levetiracetam tablet (with the exception of Study N159 which used the Keppra oral solution). One bioequivalence study of the levetiracetam tablet versus the oral solution (Keppra tablet versus oral solution) [16] and 1 in vitro study of [redacted] were also summarized by the sponsor.

Overall, the body of evidence for the review included 7 trials.

Three trials (N051,[18] N132,[19] and N138[20]) were conducted in adult patients 16 years to 70 years of age with refractory partial onset epilepsy.

Two trials (N159[21] and N1009[22]) were conducted in pediatric patients (aged 1 month to 16 years) with refractory partial onset epilepsy.

Two trials (N166[23] and N1057[24]) were conducted in a mixed population of pediatric and adult patients (aged 4 years to 65 years) with refractory generalized myoclonic or generalized tonic-clonic epilepsy.

Of the 7 randomized controlled trials (RCTs), 6 (N051, N132, N138, N159, N166, and N1057) were multi-centre, double-blind, parallel group, randomized, placebo-controlled, phase III trials and investigated the efficacy and safety of levetiracetam tablet (Keppra tablet, UCB) given as adjunctive therapy (i.e., added on to a background regimen of 1 to 3 AEDs) in patients aged 4 years to 70 years for the treatment of refractory epilepsy. Study N1009[22] was an RCT that investigated the levetiracetam oral solution (the reference product, Keppra oral solution,100 mg/mL) for the treatment of patients with refractory partial onset epilepsy who were aged 1 month to 4 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 Study N1009, the dose of levetiracetam oral solution was determined by the patient's age. The duration of the double-blind evaluation period in studies N051, N132, N138, N159, N166, and N1057 was from 12 to 20 weeks; the duration of treatment in Study N1009 was 5 days. In 5 trials (N051,[18] N132,[19] N138,[20] N159,[21] and N1057 [24]), the primary efficacy outcome was the change from baseline in reduction of the seizure frequency per week. In 2 trials (N1009[22] and N166[23]), the primary

outcome was the proportion patients who achieved a 50% or greater reduction of seizure frequency (i.e., the responder) at the end of the trial.

Efficacy Results

Adult Population (Aged 16 Years to 70 Years)

In Study N051,[18] in the treatment of adult patients with refractory partial seizures, a statistically significant greater response in the primary end point of the reduction of seizure frequency was observed at week 12 in the levetiracetam 1,000 mg/day group than in the placebo group (least squares mean [LSM] 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 than in the placebo group (mean between-group difference [levetiracetam minus placebo] = 17.7%; 98% CI, 4.1 to 29.4; P = 0.003) (Table 2). In terms of the proportion of patients who achieved a 50% or greater reduction of seizure frequency (i.e., considered responders), 22.8%, 31.6%, and 10.4% of patients were considered to be responders in the levetiracetam 1,000 mg/day group, levetiracetam 2000 mg/day group, and placebo group, respectively (Table 2).

In Study N132,[19] in the treatment of adult patients with refractory partial seizures, a statistically significant greater response in the reduction of seizure frequency was observed at week 18 in the levetiracetam 1,000 mg/day group than in the placebo group (median between-treatment group difference [levetiracetam minus placebo] = 26.1%; P < 0.001), and in the levetiracetam 3,000 mg/day group than in the placebo group (median between-treatment group difference [levetiracetam minus placebo] = 30.1%; P = 0.001) (Table 2). CIs were not reported in the sponsor's summary of the evidence. In terms of the proportion of patients who achieved a 50% or greater reduction of seizure frequency (i.e., considered responders), 37.1%, 39.6%, and 7.4% of patients were considered to be responders in the levetiracetam 1,000 mg/day group, levetiracetam 3,000 mg/day group, and placebo group, respectively (Table 2).

In Study N138,[20] in the treatment of adult patients with refractory partial seizures, a statistically significant greater response in terms of the reduction of seizure frequency was observed from baseline to the add-on phase in the levetiracetam 3,000 mg/day group than in the placebo group (median between-treatment group difference [levetiracetam minus placebo] = 22.9%; 98% CI, 14.3 to 29.4; P < 0.001). In terms of the proportion of patients who achieved a 50% or greater reduction of seizure frequency (i.e., considered responders), 42.1% and 16.7% of patients were considered to be responders in the levetiracetam 3,000 mg/day group and placebo group, respectively (Table 2).

Overall, 3 trials (N051, N132, and N138)[18-20] 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.

Pediatric Population (Aged 1 Month to 16 Years)

In Study N159 (children, aged 4 years to 16 years)[21], a statistically significant greater reduction in seizure frequency per week (the primary end point) was observed at week 14 in the levetiracetam 60 mg/kg per day group compared with the placebo group (median between-group difference [levetiracetam 60 mg/kg per day minus placebo]: 26.8%; 95% CI, 14 to 37.6; P = 0.0002; Table 2). In terms of the proportion of patients who achieved a 50% or greater reduction of seizure frequency (i.e., considered responders), 44.6% and 19.6% of

patients were considered to be responders in the levetiracetam 60 mg/day group and placebo group, respectively (Table 2).

In Study N1009 (children aged 1 month to < 4 years),[22] the dose of levetiracetam oral solution (Keppra oral solution, UCB) was determined according to age: for those aged 1 month to less than 6 months, levetiracetam was started at 20 mg/kg per day on day 1 and maintained at 40 mg/kg per day; for those aged 6 months to less than 4 years, levetiracetam was started at 25 mg/kg per day on day 1 and maintained at 50 mg/kg per day at the end of 5 days. In terms of the proportion of patients that achieved a 50% or greater reduction of seizure frequency (the primary end point), a statistically significant greater proportion of patients were considered responders on day 5 in the levetiracetam group than in the placebo group (levetiracetam oral solution versus placebo: 43.1% versus 19.6%; odds ratio [OR] = 3.11; 95% CI, 1.22 to 8.26; P < 0.013) (Table 2). This was the only study using an levetiracetam oral solution.

Studies Including a Mixed Population of Children and Adults (Aged 4 Years to 65 Years)

In Study N166,[23] in the treatment of patients aged 12 years to 65 years with refractory myoclonic seizures and of children with JME, the proportion of patients who achieved a 50% or greater reduction of seizure frequency (the primary end point) at 16 weeks was statistically significantly greater in the levetiracetam 3,000 mg/day group than in placebo group (levetiracetam 3,000 mg/day versus placebo = 58.3% versus 23.3%; OR = 4.77; 95% CI: 2.12 to 10.77; P < 0.001) (Table 2) .

In Study N1057,[24] in the treatment of patients aged 4 years to 65 years with idiopathic generalized epilepsy experiencing refractory generalized tonic-clonic seizures, a statistically significant greater response in terms of the reduction of seizure frequency (the primary end point) was observed at 24 weeks in the levetiracetam 3,000 mg/day group than in the placebo group (as reported in Health Canada review report, the LSM between-treatment group difference [levetiracetam 3,000 mg/day minus placebo]: 28.31%; 95% CI, 8.97 to 47.64; P = 0.004) (Table 2).[13] In terms of the proportion of patients who achieved a 50% or greater reduction of seizure frequency (i.e., considered responders), 68.4% and 44.0% of patients were considered to be responders in the levetiracetam 3,000 mg/day group and placebo group, respectively (Table 2).

Harms Results

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

Across the 7 included studies, the proportion of the patients experienced at least 1 treatment-emergent adverse event (TEAE) were largely similar between levetiracetam and placebo arms, and appeared to be similar across the studies in adults and children. Overall, the most frequently reported TEAEs were somnolence, agitation, depression, nasopharyngitis, headache, fatigue, anorexia, and dizziness. The clinical expert consulted for this review indicated that the AEs reported in the included trials are aligned with what is expected in clinical practice.

The percentage of patients experiencing at least 1 serious adverse event (SAE) and the most common SAEs were not available in the sponsor's summary of evidence for all of the studies. The same is true for the data presented regarding withdrawals due to AEs. Information pertaining to AEs 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 reactions, as well as anorexia and decreased appetite, which were more common in children than in adults.[9]

There were no deaths reported during the treatment periods of the all included trials except that in N132.[19] In Study N132, 2 deaths were reported.

Table 2: Key Outcomes (ITT)[a]

Treatment groups	Reduction in seizure frequency (weekly, %)						Proportion of patients with ≥ 50% reduction (%)			
	N	Baseline	End of treatment		Between-group difference (LEV vs. placebo)		N	End of treatment	LEV vs. placebo	
		Median (SD)	Median (SD)	MCFB (SE)	Median/mean difference (95% CI)	P value		% of patients	OR (95% CI)	P value
Studies in adults (16 years to 70 years)										
Study N051, Shorvon et al. (2000) – 12 weeks evaluation time										
LEV 1,000 mg/day	106	2.82	NR	17.7[b]	LSM[c] = 16.4 (98% CI, 2.7 to 28.1)	0.006	101	22.8	NR[d]	< 0.02
LEV 2,000 mg/day	106	2.58	NR	26.5[b]	Mean[c] = 17.7 (98% CI, 4.1 to 29.4)	0.003	95	31.6	NR[d]	< 0.001
Placebo	112	2.50	NR	6.1[b]	NR	NR	106	10.4	NR	NR
Study N132, Cereghino et al. (2000) – at 18 weeks evaluation period plus titration										
LEV 1,000 mg/day	98	2.53	NR	36.9	Median = 26.1	< 0.001	98	37.1	NR	< 0.001
LEV 3,000 mg/day	101	2.08	NR	38.1	Median = 30.1	< 0.001	101	39.6	NR	< 0.001
Placebo	95	1.77	NR	6.9	NR	NR	95	7.4	NR	NR
Study N138, Ben-Menachem et al. (2000) – from baseline to add-on phase										
LEV 3,000 mg/day	181	1.69	NR	39.9	Median = 22.9 (98% CI, 14.3 to 29.4)	< 0.001	181	42.1	NR	< 0.001
Placebo	105	1.75	NR	7.2	NR	NR	105	16.7	NR	NR
Studies in children (1 month to 16 years)										
Study N159, Glauser et al. (2009) – evaluation period 14 weeks										
LEV 60 mg/kg per day	101	4.7	NR	43.8	Median = 26.8 (14 to 37.6)	0.0002	101	44.6	3.3 (1.75 to 6.24)	0.0002
Placebo	97	5.3	NR	23.3	NR	NR	97	19.6	NR	NR

Treatment groups	Reduction in seizure frequency (weekly, %)						Proportion of patients with ≥ 50% reduction (%)			
	N	Baseline	End of treatment		Between-group difference (LEV vs. placebo)		N	End of treatment	LEV vs. placebo	
		Median (SD)	Median (SD)	MCFB (SE)	Median/mean difference (95% CI)	P value		% of patients	OR (95% CI)	P value
Study N1009, Pina-Garza et al. (2009) – evaluation period 5 days										
LEV oral solution[e]	NR	NR	NR	NR	NR	NR	58 (mITT)[a]	43.1	3.11 (1.22 to 8.26) mITT)[f]	0.013
Placebo	NR	NR	NR	NR	NR	NR	51 (mITT)	19.6	NR	NR
Studies in a mixed population of children and adults (4 years to 65 years)										
Study N166, Noachtar et al. (2008) – 16 weeks evaluation period										
LEV 3,000 mg/day	NR	NR	NR	NR	NR	NR	60	58.3	4.77 (2.12 to 10.77)	0.001
Placebo	NR	NR	NR	NR	NR	NR	60	23.3	NR	NR
Study N1057, Berkovic et al. (2009) – 24 weeks evaluation period plus titration										
LEV[g]	78	0.62 (mean = 1.70)	NR	77.8 (mean = 56.49)[h] (77.6)[i]	LSM = 28.31 (8.97 to 47.64)[h]	0.0004[h]	79	68.4 (77.2)[i]	3.28 (1.68 to 6.38)[i]	0.004
Placebo	84	0.62 (mean = 1.20)	NR	47.7 (mean = 28.19)[h] (44.6)[i]	NR	NR	74	44.0 (45.2)[i]	NR	NR

CI = confidence interval; diff = difference; EEG = electroencephalogram; ITT = intention to treat; LEV = levetiracetam; LSM = least squares mean; MCFB = median change from baseline; mITT = modified intention-to-treat population; NR = not reported; OR = odds ratio; SD = standard deviation; SE = standard error; vs. = versus.

[a] ITT analyses were performed in all except 2 trials (N1009[22] and N132[19]). In 5 trials using ITT (N051, N138, N159, N166, and N1057), although the ITT population was defined as an analysis that included all randomized patients who received at least 1 dose of the study drug, which was technically a mITT population due to the requirement to have had at least 1 dose of study medication. Nonetheless, all randomized patients except 1 patient in Study N166 and 2 patients in Study N1057 were included in the ITT populations (i.e., all randomized patients except 1 patient in Study N166 and 2 patients in Study N1057, see Table 12) and took at least 1dose of the study drug. In Study 1009, the mITT population included all ITT patients who had at least 24 hours of usable baseline video EEG and at least 24 hours of evaluation of video EEG, and also included any randomized subjects who withdrew before the first 24 hours of evaluation video EEG, with reasons linked to lack or loss of efficacy (nonresponders for the primary efficacy end point).[22] In Study N132, the main analysis was based on patients completing the titration period (in addition to responder analysis in all randomized patients).[19]

[b] All partial subtypes (simple and complex).

[c] LSM difference: Reduction over placebo: back transformation of the difference of log seizure frequency between LEV 1,000 mg/day or 2,000 mg/day and placebo, expressed in percent of placebo = 100 [I - exp (LSM LEV- LSM placebo)].

[d] The number of patients needed to treat to get a responder with a 50% or greater reduction in seizure frequency during treatment with LEV was 6.9 (95% CI, 4.3 to 17.9) for the 1,000 mg group and 3.5 (95% CI, 2.6 to 5.4) for the 2,000 mg group. In addition, 3.7% of patients in the placebo group experienced a 75% or greater reduction in seizure frequency, compared with 10.9% (P = 0.03) for the 1,000 mg group and 16.8% (P = 0.001) for the 2000 mg group. Five patients (5%) in the 1,000 mg group and 2 patients (2%) in the 2,000 mg group were seizure free during the evaluation period, compared with 1 patient (0.9%) in the placebo group who reported no seizures until study withdrawal at day 29.[14]

[e] The 10% oral solution (100 mg/mL). For age 1 month to less than 6 months, LEV was started at 20 mg/kg per day on day 1 and maintained at 40 mg/kg per day. For age 6 months to less than 4 years, LEV was started at 25 mg/kg per day on day 1 and maintained at 50 mg/kg per day.

[f] The results were consistent across all age groups (Figure 3), although a slightly higher responder rate and OR were observed in the subgroup of infants aged 1 month to less than 12 months than in other subgroups (OR = 4.8; 95% CI, 0.5 to 62.3, compared with OR = 2.7; 95% CI, 0.5 to 15.4 for the 12 month to less than 24 months age group, and OR = 2.9; 95% CI, 0.7 to 14.7 for the 24 month to less than 48 month age group).

[g] Dosing in adults, LEV 3,000 mg/day and in children, LEV 60 mg/kg per day during the 20-week evaluation phase.

[h] Data from Health Canada reviewer report added by CADTH.

[i] During the evaluation period (20 weeks, LEV 3,000 mg/day in adults and LEV 60 mg/kg per day in children), the median reduction of the seizure frequency in the LEV group was 77.8% vs. 47.7% in the placebo group (P < 0.001); the percentage of responders in the LEV group was 68.4% vs. 44.0% in the placebo group (P < 0.001). In the treatment period (24-week titration plus evaluation period, LEV 1,000 mg to 3,000 mg/day in adult sand LEV 20 mg/kg to 60 mg/kg per day in children), the median reduction of the seizure frequency in the LEV group was 77.6% vs. 44.6% in the placebo group (P < 0.001); the percentage of responders in the LEV group was 72.2% vs. 45.2% in the placebo group (P < 0.001). The OR (95% CI) for the treatment period (24-week titration plus evaluation period) was 3.28 (1.68 to 6.38).[24]

Source: Shorvon et al.,[18] Cereghino et al.,[19] Ben-Menachem et al.,[20] Glauser et al.,[21] Pina-Garza et al.,[22] Noachtar et al.,[23] Berkovic et al.[13,24]

Critical Appraisal

Although detailed information of the methodology of the included clinical trials was not available, the overall design of each trial appears to be appropriate with respect to randomization, blinding, allocation concealment, and standardized assessment of the primary outcomes.

Based on the information available in the sponsor's summary of the clinical evidence, each trial appeared to be generally well balanced in terms of baseline demographic and disease characteristics.

Except for Study N1009,[22] in the remaining 6 trials, the seizure frequency and seizure types were recorded by patients, and/or caregivers or legal guardians by filling in a daily record card which was returned at each study visit.[18-21,23,24] Although this is a standard method of reporting outcomes related to seizure frequency in clinical trials of AEDs, patient- or caregiver-reported outcomes are subject to individual variability in reporting accuracy (e.g., missing or misclassification of seizures) and completion.

None of the trials included in the summary of clinical evidence provided by the sponsor were conducted using the formulation of the product under review (pdp-levETIRAcetam), which is acceptable for dugs reviewed through Health Canada's Submissions Relying on Third-Party Data pathway. Of the 7 included pivotal trials, only 1 trial (N1009)[22] was conducted using the levetiracetam oral solution (Keppra oral solution, UCB), but this study was only 5 days in duration and included only pediatric patients.[16] No direct comparative clinical trials were included in the sponsor's submission that compared levetiracetam oral solution with levetiracetam tablets. To fill this evidence gap, the sponsor provided bioequivalence and physiochemistry test data.

Despite the various generalizability issues (such as history of previous treatment in the study population and treatment duration during the study), overall baseline characteristics were generally well balanced between treatment groups in each study. The clinical expert consulted for this review indicated that the baseline demographic and disease characteristics of the patients enrolled in the 7 trials are generally representative of patients with refractory epilepsy seen in clinical practice in Canada.

No evidence comparing levetiracetam with other existing AEDs was summarized by the sponsor. However, according to the expert consulted by CADTH for this review, it is generally accepted that all AEDs are of similar efficacy, but levetiracetam appears to be associated with an improved tolerability profile. Furthermore, the clinical expert consulted in the review indicated that this lack of comparative data would be unlikely to influence prescribing of levetiracetam oral solution.

Conclusions

Based on the summary of clinical evidence submitted by the sponsor, compared with placebo, levetiracetam tablets (Keppra tablets, UCB) used as adjunctive treatment demonstrated a greater reduction in seizure frequency in adult (16 years to 70 years) and pediatric (4 years to 16 years) patients with refractory epilepsy. In addition, a greater proportion of patients treated with levetiracetam were considered responders (i.e., achieved a 50% or greater reduction of seizure frequency) than in the placebo group. In 1 study conducted in children aged 1 month to less than 4 years, adjunctive treatment with levetiracetam oral solution (Keppra oral solution, UCB) resulted in a greater proportion of patients achieving a 50% or greater reduction of seizure frequency than in the placebo group.

The sponsor's summary of evidence was based on third-party data and only published studies were available. Despite the lack of methodological detail, the studies appear to be well conducted. Further, the clinical expert consulted for this review indicated that the findings of the clinical efficacy and AEs reported in the included trials were aligned with what would be expected in Canadian clinical practice.

At the submitted price based on the recommended daily dose of 1,000 mg per day, levetiracetam oral solution was associated with increased annual expenditures of $2,340 per patient when compared with the compounded suspension and $2,686 per patient when compared to levetiracetam oral tablets. However, there was variability in the list prices for levetiracetam among jurisdictions and the recommended dosing according to each patient population that influence annual cost estimates.

Introduction

Disease Background

Epilepsy is a chronic neurological disorder that is defined by at least 2 unprovoked seizures occurring more than 24 hours apart, 1 unprovoked seizure and a probability of further seizures that is similar to the general recurrence risk after 2 unprovoked seizures (at least 60%, occurring over the next 10 years), or a diagnosis of an epilepsy syndrome.[1] An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive and or synchronous neuronal activity in the brain.[7] The term "unprovoked seizure" refers to a seizure of unknown etiology as well as one that occurs in relation to a pre-existing brain lesion or progressive nervous system disorder.[25] The ILAE classifies epilepsy based on seizure type, epilepsy type, and epilepsy syndrome.[2] Seizure types are classified as generalized onset, focal (or partial) onset, or unknown onset. Epilepsy types include generalized, focal, combined generalized and focal, and unknown epilepsy.[2] Generalized seizure types include generalized tonic-clonic, myoclonic, absence, tonic, clonic, and atonic. A partial seizure can evolve over seconds into a bilateral tonic-clonic seizure, also referred to as a secondarily generalized seizure.[8] Childhood absence epilepsy, JME, or epilepsy with grand mal seizures on awakening are examples of epilepsy syndromes in which multiple seizure types may be present.[24,14] The onset and diagnosis of epilepsy is most common during childhood.[13] The clinical expert consulted by CADTH for this review indicated that a diagnosis of epilepsy is based on the presence of 2 or more unprovoked seizures or 1 unprovoked seizure and evidence suggesting significant recurrence rate and that most often diagnosis is relatively straightforward.

Epilepsy is associated with an increased risk of a variety of psychiatric and medical comorbidities that can adversely impact quality of life as well as life expectancy.[3] Comorbidities (e.g., gastrointestinal ulcers, stroke, urinary incontinence, bowel disorders, and psychiatric disorders) can arise due to common underlying predispositions, direct effects of seizures, underlying epilepsy etiologies, and adverse effects of antiseizure drugs and other therapies.[10] Depression and anxiety are particularly common in adults with epilepsy.[14]

Approximately 0.6% of the Canadian population has epilepsy.[4] The reported incidence of epilepsy in the pediatric population ranges from 41 to 187 per 100,000, being highest in the first year of life and declining to adult levels by the end of the first decade.[5] Each day in Canada, an average of 42 people, or approximately 15,500 people annually, are diagnosed with epilepsy.[4] Due to the stigma surrounding epilepsy and the prejudice with which society has historically treated people with epilepsy, the prevalence of epilepsy is likely much underestimated.[4] Of these, 44% are diagnosed before the age of 5, 55% before age 10, 75% to 85% before age 18. Approximately 1% of children will have recurrent seizures before age 14, and 1.3% after the age of 60 years.[4]

Epilepsy is considered as medically refractory epilepsy (or drug-resistant epilepsy, pharmacoresistant epilepsy, or intractable epilepsy) when a patient fails to achieve sustained seizure freedom after adequate trials of 2 tolerated AEDs (either monotherapies or in combination).[6] Approximately 20% to 40% of patients with epilepsy are likely to have refractory epilepsy.[6,7]

Standards of Therapy

The goals of epilepsy treatment are to control seizures, avoid AEs, and maintain or restore HRQoL.[8] The clinical expert consulted by CADTH indicated that the ideal antiseizure medication would reduce seizure frequency to 0 without adverse effects. The goals of reducing the frequency of seizures or eliminating them would be to:

- improve HRQoL
- improve cognitive function
- reduce hospitalization and emergency room visits
- reduce the use of emergency rescue medications for seizures
- improve likelihood of employment
- reduce burden on caregivers.

The treatment paradigm for epilepsy begins with antiseizure medications. Typically, treatment is initiated with 1 medication and if not effective or side effects are not tolerable, a second medication is initiated as adjunctive or monotherapy. With treatment, approximately 30% to 50% of the patients with a new diagnosis of epilepsy will become seizure free with the first AED prescribed.[8] Of those whose initial therapy is ineffective, about 10% to 20% will have a successful second drug trial.[8,13,4] For patients with refractory epilepsy, most often further medications will be tried and, as appropriate, other therapies considered, such as surgery. Combination therapy with 2 or more AEDs may be required for some patients whose epilepsy is refractory (i.e., treatment-resistant).[6] The selection of AEDs is individualized for each patient based on various factors which include the effectiveness of the drug for the patient's seizure type, potential AEs, and interactions with medications, comorbid medical conditions, age, patient preference, and cost.[8]

Levetiracetam is a drug of the pyrrolidine class. As with other drugs in this class, the mechanism of action of levetiracetam is not known.[9] Levetiracetam is a broad spectrum antiseizure medication and has shown to be effective for control of various seizure types in both adults and children with epilepsy.[10-12] Until recently, the only oral formulation of levetiracetam approved by Health Canada was the tablet which is indicated as adjunctive therapy for the management of adults with epilepsy who have not responded to conventional therapy.[10] However, due to the favourable efficacy and safety profile, clinically, levetiracetam tablet is often prescribed as a first-line treatment for pediatric patients with epilepsy.[7,13] In the absence of availability of an oral solution, levetiracetam oral suspension (50 mg/mL) has been compounded and used for patients (adult and children) who are not able to swallow levetiracetam tablets.[13,14] In the US and EU, levetiracetam tablets[15] and oral solution[16] have been marketed for more than 10 years in the treatment of patients with refractory epilepsy in adults and for pediatric patients with partial onset seizures, myoclonic seizure, and generalized tonic-clonic seizures.

As noted in a previous CADTH report:

> Levetiracetam tablet 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.[10]

Drug

The focus of the CADTH review is the levetiracetam oral solution (pdp-levETIRAcetam) only.

Levetiracetam oral solution (pdp-levETIRAcetam oral solution, 100 mg/mL)[9] was approved by Health Canada in July 2019. For adults, it is indicated as adjunctive therapy in the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy. For pediatrics, it is indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalization in adolescents, children, and infants (from 1 month of age) with epilepsy; myoclonic seizures in adolescents from 12 years of age with JME; and PGTC seizures in adolescents from 12 years of age with idiopathic generalized epilepsy.[9] It is available as 100 mg/mL in a 300 mL amber glass bottle with a child-resistant screw cap.

The Health Canada-recommended dose for add-on therapy in adults (> 18 years) and adolescents (12 years to 17 years) weighing 50 kg or more is as follows: treatment should be initiated at a dose of 1,000 mg/day, given as twice-daily dosing (500 mg twice-daily). Depending on the clinical response and tolerability, the daily dose may be increased every 2 weeks by increments of 1,000 mg, to a maximum recommended daily dose of 3,000 mg (1,500 mg twice daily).[9] There are limited safety data from controlled clinical trials at doses higher than 3,000 mg/day (approximately 40 patients), therefore these doses are not recommended.[9]

Based on the Health Canada product monograph, pdp-levETIRAcetam oral solution is the preferred formulation over tablets for use in infants and children under the age of 6 or under 25 kg, and in any patients unable to swallow tablets.[9] The recommended dose for levetiracetam oral solution differs according to age and weight in pediatric patients and is presented in Table 3 and Table 4.

For add-on therapy in infants aged 1 month to less than 6 months (Table 3), the initial therapeutic dose is 7 mg/kg twice daily.[9] Depending upon the clinical response and tolerability, the dose can be increased up to 21 mg/kg twice daily. Dose changes should not exceed increases or decreases of 7 mg/kg twice daily every 2 weeks. The lowest effective dose should be used. Infants should start the treatment with pdp-levETIRAcetam 100 mg/mL oral solution. To ensure the accuracy of dosing for this age group, administer the oral solution using a 1 mL dosing syringe.

Table 3: Dose Recommendations for Infants Aged 1 Month to < 6 Months

Weight	Starting dose 7 mg/kg twice daily	Maximum dose 21 mg/kg twice daily
4 kg	28 mg (0.3 mL) twice daily	84 mg (0.85 mL) twice daily
5 kg	35 mg (0.35 mL) twice daily	105 mg (1.05 mL) twice daily
7 kg	49 mg (0.5 mL) twice daily	147 mg (1.5 mL) twice daily

Source: pdp-levETIRAcetam product monograph.[9]

For add-on therapy in infants aged 6 months to less than 4 years, children aged 4 years to 11 years, and adolescents aged 12 to 17 years weighing less than 50 kg (Table 4),[9] the initial therapeutic dose is 10 mg/kg twice daily.[9] Depending upon the clinical response and tolerability, the dose can be increased up to 30 mg/kg twice daily. Dose changes should not exceed increases or decreases of 10 mg/kg twice daily every 2 weeks. The lowest effective dose should be used. For adolescents aged 12 years to 17 years weighing 50 kg or more, see adult dosing recommendations.

Table 4: Dose Recommendations for Infants (Aged 6 Months to < 4 Years) and for Children (Aged 4 Years to 11 Years) and Adolescents (Aged 12 Years to 17 Years) Weighing Less Than 50 kg

Weight	Starting dose 10 mg/kg twice daily	Maximum dose 30 mg/kg twice daily
6 kg[a]	60 mg twice daily	180 mg twice daily
10 kg[a]	100 mg twice daily	300 mg twice daily
15 kg[a]	150 mg twice daily	450 mg twice daily
20 kg[a]	200 mg twice daily	600 mg twice daily
25 kg	250 mg twice daily	750 mg twice daily
From 50 kg[b]	500 mg twice daily	1,500 mg twice daily

[a] Children 25 kg or less should preferably start the treatment with pdp-levETIRAcetam 100 mg/mL oral solution.

[b] Dose in children and adolescents 50 kg or more is the same as in adults.

Source: pdp-levETIRAcetam product monograph.[9]

Stakeholder Engagement

Patient Group Input

This section was prepared by CADTH staff based on the input provided by GPFC. The GPFC is not a patient group or association, but has a team of clinicians who work closely with patients and has shared their views on the importance of the commercial availability of levetiracetam oral solution.

About the GPFC and Information Gathered

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 Centre Hospitalier Universitaire Sainte-Justine Hospital Foundation. Pharmascience and Pendopharm are fully owned by the Goodman family. Although the GPFC supported the commercialization of levetiracetam by providing services to Pharmascience and Pendopharm, the GPFC has a strict governance structure to ensure that GPFC operates completely independently from all their industry partners. GPFC indicated that their opinions are solely theirs. In addition, the information submitted to CADTH was written by GPFC and was not reviewed by anyone outside of the GPFC.

The GPFC has the goal of improving access to child-friendly medicines. GPFC indicated that they are the only centre in Canada whose mandate is to assist in the development of safe and effective age-appropriate formulations for children. The GPFC operates as a not-for-profit organization, with the exclusive goal to support the well-being of children by facilitating the availability of formulations adapted to their needs for optimal treatment. Even though the GPFC works closely with hospitals, health care providers, and industry, GPFC's positions and actions are completely independent of these third parties.

In their submission, the GPFC provided reasons why they thought access to the commercial oral solution of levetiracetam is important for Canadian children, as follows:

Children differ from adults in many aspects that may affect pharmacotherapy, including drug disposition and toxicity, and the capabilities for drug administration. Numerous medications given to children have no commercially available, age-appropriate pharmaceutical forms, leading to many challenges including manipulation of dosage forms designed for adults by health care professionals and parents. The lack of suitable pediatric formulations leaves children at increased risk of adverse events, suboptimal dosing with consequent risk of therapeutic failure, noncompliance due to palatability issues and limited access to new medicines (which are rarely formulated for children).

Levetiracetam, is a widely used antiepileptic drug (AED) in children. Levetiracetam, a second-generation AED, has been shown to be effective and safe in children as young as 1 month of age with different seizure types. It has a low potential for clinically relevant drug interactions, a good tolerability, a favourable pharmacokinetic (PK) profile, and is available as oral formulations. All these attractive properties explain why levetiracetam is increasingly used in Canadian children who suffer from seizures. In Canada, oral levetiracetam is given as an off-label extemporaneous suspension given the Canadian label has no pediatric indication, and no oral solution is approved. This is in contrast with the US and EU where the first pediatric indication for levetiracetam was granted in 2005. Furthermore, levetiracetam oral solution (100 mg/mL) and concentrate for IV infusion (500 mg/5 mL) have

been on the US and the EU markets for more than 10 years. This highlights how Canada has fallen behind.

Although the majority of children with epilepsy are responsive to treatment, approximately one-third will remain refractory and experience seizures despite treatment with at least 2 appropriate AEDs and frequently require polypharmacy.[17] In these patients, the interference of seizures and epileptic activity with brain maturation may lead to progressive cognitive and behavioural decline, which imposes an additional burden on families and society.[26] Within the polypharmacy required to optimize seizure control in these patients, effective AEDs with favourable benefit/risk ratios such as levetiracetam are in demand.

Today, there is no justification for levetiracetam compounding given the risks it bears and knowing a safe and efficacious oral solution exists and has been used for more than a decade in children around the world. Canadian children suffering from seizures and epilepsies deserve access AEDs with formulations adapted to their needs and meeting the highest pharmaceutical grade standards. Thus, there is an urgent need for a commercially available and publicly reimbursed oral solution formulation of levetiracetam for Canadian children.

Clinician Input

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by 1 clinical specialist with expertise in the diagnosis and management of epilepsy.

Unmet Needs

The clinical expert indicated prior to the introduction of the levetiracetam oral solution to Canadian market, many patients were using a compounded suspension of levetiracetam and that with the introduction of this product to the market, the compounded products would not likely be made by local pharmacies. As such, many children who relied on compounded liquid have 2 options — pay for this oral suspension product or crush tablets — approval of levetiracetam oral solution will fill that gap.

Place in Therapy

The clinical expert consulted for this review considered levetiracetam as appropriate for first-line treatment for epilepsy given its favourable side effect profile and broad spectrum efficacy.

Tablets are used as an oral treatment in patients who are able to swallow pills. On some occasions they are crushed for people who cannot swallow pills. Crushed tablets and oral solutions would also be used for people using a gastrostomy tube. The oral solution would be used for those people who have been using the crushed tablets.

The clinical expert anticipated that levetiracetam oral solution would be added to the current treatments available for epilepsy. As levetiracetam has been available for many years, it's place in therapy is already established, and the introduction of this formulation would not be anticipated to change the treatment landscape.

Patient Population

The clinical expert consulted by CADTH indicated that levetiracetam is effective for a broad range of seizure types and that the oral solution of levetiracetam would allow patients who are unable to tolerate tablets to use the medication. These patient populations include:

young infants and children unable to swallow tablets

adults and children with swallowing difficulties fed by gastrostomy tube.

The clinical expert stated that levetiracetam has a favourable side effect profile but is known to cause psychiatric and behavioural effects and indicated that it should be used with caution in people with pre-existing psychiatric and behavioural conditions.

Assessing Response to Treatment

The clinical expert considered reduction in seizure frequency to be the best way to determine a response to treatment and considered a clinically meaningful response to treatment to be dependent on the pre-treatment frequency of seizures. The clinical expert acknowledged that most clinical trials consider a 50% or more reduction in seizure frequency to be clinically significant, but noted that in clinical practice complete seizure freedom is the goal. The response of the treatment is usually assessed every 6 months. The clinical expert indicated that in clinical practice, patients would be considered to be responsive to treatment if they were seizure free for a minimum of 3 times the interseizure interval or 12 months.

Discontinuing Treatment

The clinical expert consulted by CADTH indicated that the typical approach in Canadian practice is to withdraw medication once the patient has been seizure free for 2 years or if the medication is not effective after an adequate trial.

Prescribing Conditions

The clinical expert indicated that levetiracetam oral solution could be used in community and hospital settings and that it may be prescribed by primary care physicians.

Sponsor's Summary of the Clinical Evidence

Note that the clinical evidence summarized in this section was prepared by the sponsor in accordance with the CADTH tailored review process and has not been modified by CADTH.

Pivotal Studies

Pendopharm reached out to CADTH for guidance on the correct way to complete the following table because levetiracetam has been available for more than 10 years in Canada and internationally. On June 16, 2020, CADTH advised that we focus on the clinical studies that are referenced in the approved product monograph for pdp-levETIRAcetam. Below are listed the adult and pediatric pivotal trials from the product monograph. (CADTH, Ottawa, Ont: personal communication, June 16, 2020)

Table 5: Details of Included Studies (Adults): Add-On Therapy for Refractory Partial Seizures

Detail	Study N051 Shorvon et al. (2000)[18]	Study N132 Cereghino et al. (2000)[19]	Study N138 Ben-Menachem et al. (2000)[20]
Designs and populations			
Study design	Multi-centre, double-blind, randomized, placebo-controlled safety and efficacy trial	Multi-centre, double-blind, randomized, placebo-controlled, parallel group safety and efficacy trial	Multi-centre, double-blind, placebo-controlled, parallel group, responder-selected study
Locations	61 sites in Belgium, France, Germany, Luxembourg, Switzerland, and the UK	US	47 institutions throughout Europe
Randomized (N)	Male: 157 Female: 167	Male: 178 Female: 116	Male: 137 Female: 149
Inclusion criteria	• 16 years to 65 years • Refractory epilepsy • Seizures that were only or predominantly partial, with or without SG • Seizures that had persisted for at least the previous 2 years despite treatment with 1 or 2 AEDs • Maintained stable dose regimens of a maximum of 2 AED for at least 4 weeks before the selection visit, as well as throughout the study • ≥ 4 partial seizures during each 4-week interval in the 8- or 12-week baseline period	• 16 years to 70 years • Uncontrolled partial seizures with or without becoming secondarily generalized for at least 2 years • Minimum of 12 partial seizures within 12 weeks before study selection, with a minimum of 2 partial seizures occurring per 4 weeks during the baseline period • Patients must have received at least 2 marketed AEDs, either simultaneously or consecutively	• 16 years to 70 years • Clinically observed partial seizures for at least a year before study entry • At least 2 complex partial seizures per 4 weeks during baseline despite treatment with 1 AED

Detail	Study N051 Shorvon et al. (2000)[18]	Study N132 Cereghino et al. (2000)[19]	Study N138 Ben-Menachem et al. (2000)[20]
Exclusion criteria	• Patients with renal insufficiency • Progressive neurologic disorders • Serious psychiatric disorders • Clinically significant baseline laboratory abnormalities • Current or recent history of substance abuse • Questionable compliance with drug treatment • Concomitant disorders	• Medical conditions other than epilepsy or with chronic progressive neurologic disease • Participation in other investigational drug trial within the 4 weeks preceding study entry • History of drug or alcohol abuse, or had impairments in renal or hepatic function	• History of status epilepticus or a seizure pattern characterized by clusters during the previous 5 years and the 12-week baseline period • History of CNS or cardiovascular or other disorders • No participation in any other clinical trial within the 4 weeks preceding study entry
Drugs			
Intervention	**Oral tablets** **Treatment** • LEV 1,000 mg/day (500 mg b.i.d.) • LEV 2,000 mg/day (1,000 mg b.i.d.)	**Oral tablets** **Treatment** • LEV 1,000 mg/day • LEV 3,000 mg/day	**Oral tablets** **Treatments** • Oral LEV 1,500 mg b.i.d.
Comparator(s)	Placebo	Placebo	Placebo
Duration			
Phase	NA	NA	NA
Run-in	• Baseline period of 8 weeks • Study drug initiation: LEV was titrated upward in twice-daily increments of 500 mg at 2-week intervals until patients were stabilized on their assigned dosages • The 1,000 mg group received placebo for 2 weeks before initiation of active drug	• 12-week, single-blind, placebo baseline period • 4-week double-blind drug titration period	12-week baseline period
Double-blind	Treatment continued for the 12-week evaluation period	14-week double-blind treatment period	18-week, double-blind, add-on therapy phase that included 4 weeks of up-titration of either LEV or placebo, and a monotherapy phase that included a maximum of 12 weeks of down-titration and 12 weeks of monotherapy

Detail	Study N051 Shorvon et al. (2000)[18]	Study N132 Cereghino et al. (2000)[19]	Study N138 Ben-Menachem et al. (2000)[20]
Follow-up	NA	• 8-week double-blind study medication withdrawal period or the possibility of entering an open follow-up study • Possibility to enter a 1 year follow-up study	Long-term follow-up or down-titration after week 54
Outcomes			
Primary end point	Mean number of partial seizures per week	Mean number of partial seizures per week	Monotherapy phase 1. Percentage of patients who completed the monotherapy phase relative to the number of patients randomized to receive study medication Add-on phase 2. Number of partial seizures per week 3. Responder rate
Secondary and exploratory end points	• Median % reduction in seizure frequency from baseline for all seizure types and subtypes • Responder rate: % patients with ≥ 50% reduction in partial seizure frequency and ≥ 75% reduction in partial seizure frequency • Incidence of seizure-free patients	• Median % reduction compared to baseline • Responder rate (number of patients with a minimum of 50% reduction from baseline in partial seizure frequency) • Number of seizure-free patients	NA
Notes			
Publications	Shorvon et al. (2000) Clinicaltrials.gov number unknown	Cereghino et al. (2000) Clinicaltrials.gov number unknown	Ben-Menachem et al. (2000) Clinicaltrials.gov number unknown

AED = antiepileptic drug; b.i.d. = twice a day; CNS = central nervous system; LEV = levetiracetam; NA = not applicable; SG = secondary generalization.

Source: Shorvon et al. (2000), Cereghino et al. (2000), Ben-Menachem et al. (2000).[18-20]

Table 6: Details of Included Studies: Children, Adolescents, and Adults

Detail	Partial onset seizures		Myoclonic seizures	GTC seizures
	Study N159 Glauser et al. (2006)[21]	Study N1009 Pina-Garza et al. (2009)[22]	Study N166 Noachtar et al. (2008)[23]	Study N1057 Berkovic et al. (2007)[24]
Designs and populations				
Study design	Randomized, placebo-controlled, double-blind, parallel group trial	Multi-centre, double-blind, randomized, placebo-controlled study	Randomized, double-blind, placebo-controlled, multi-centre trial	Randomized, double-blind, placebo-controlled, parallel group study
Locations	60 centres in the US and Canada	62 centres in 13 countries (Belgium, Brazil, Czech Republic, France, Germany, Hungary, Italy, Mexico, Poland, Romania, Russia, UK, and US).	37 centres in 14 countries (Australia, New Zealand, Europe, and North and Central America)	50 centres in Europe, North America, Mexico, Australia, and New Zealand
Randomized (N)	216	116	122	164
Inclusion criteria	• 4 years to 16 years • Weighing 13.5 to 80 kg (30 to 177 lb) • Partial seizures • Inadequately controlled with 1 or 2 concomitant AEDs • At least 4 partial seizures during the 4 weeks preceding the screening visit and at least 4 partial seizures during each 4-week interval of the 8-week baseline period	• 1 month to < 4 years and weighing ≥ 4.0 kg • ≥ 2 partial onset seizures, with/without secondary generalization • Subjects 1 month to < 6 months of age with ≥ 2 partial onset seizures during the baseline with/without corresponding clinical event • Subjects aged 6 months to < 4 years with ≥ 2 partial onset seizures during the baseline with corresponding clinical event • Patients maintained on a stable regimen of 1 or 2 concomitant AEDs for the selection and evaluation periods	• 12 years to 65 years • Diagnosis of IGE with myoclonic seizures on ≥ 8 days during the study baseline period, and were receiving a stable dose of 1 AED for ≥ 4 weeks before study entry • Absence of evidence of brain lesions (CT scan or MRI), and diagnosis of JME, JAE, or epilepsy with GTC seizures on awakening	• 4 years to 65 years • Weight ≥ 20 kg • Electroclinical diagnosis consistent with IGE, who were experiencing GTC seizures despite treatment with 1 or 2 AEDs • ≥ 3 GTC seizures during the 8-week combined baseline period • ≥ 1 seizure during both the historical and prospective baseline periods and CT or MRI done in the last 5 years did not show a progressive brain lesion
Exclusion criteria	• History of a treatable seizure etiology or other disorders • SE that required hospitalization 3 months before the screening visit • History of multiple drug allergies • Any medication (other than a concomitant AED) acting on the CNS	• Treatable seizure etiology • SE that required hospitalization during the month before the baseline visit • Current diagnosis of Lennox-Gastaut syndrome • Epilepsy secondary to a progressive cerebral or neurodegenerative disease • Previous use of LEV	• Nonepileptic seizures within the previous year • Signs suggestive of a progressive brain lesion • History of partial onset seizures • SE within the previous 3 months • Previous or current treatment with LEV • Current use of vigabatrin or tiagabine	• Partial onset seizures, including secondarily GTC seizures • Pseudoseizures within the last year • Seizures occurring only in clustered patterns • History of SE while taking AEDs within the 3 months before study visit 1

Detail	Partial onset seizures		Myoclonic seizures	GTC seizures
	Study N159 Glauser et al. (2006)[21]	Study N1009 Pina-Garza et al. (2009)[22]	Study N166 Noachtar et al. (2008)[23]	Study N1057 Berkovic et al. (2007)[24]
	• Use of any investigational drug or device during the 30 days before the screening visit • Use of a ketogenic diet within 30 days before the screening visit		or current use of felbamate with < 18 months exposure	
Drugs				
Intervention	**Oral tablets** LEV initiated at 20 mg/kg per day (b.i.d). Target dose of 60 mg/kg per day	**10 % oral solution (100 mg/mL)** **Age 1 month to < 6 months:** LEV started at 20 mg/kg per day on day 1; maintained at 40 mg/kg per day **Age 6 months to < 4 years:** LEV started at 25 mg/kg per day on day 1, maintained at 50 mg/kg per day	**Oral tablet** 4-week up-titrated to maintenance dose of LEV 3,000 mg/day	**Oral tablet** **Adults:** 3,000 mg/day **Children:** 60 mg/kg per day 4-week up-titration phase and a 20-week evaluation phase
Comparator(s)	Placebo	Placebo	Placebo	Placebo
Duration				
Phase	Phase III	NA	Phase III	Phase III
Run-in	8-week baseline period	• 48 hour inpatient baseline video EEG	8-week baseline period with a 4-week up-titration period	8-week baseline period (4-week retrospective and 4-week prospective)
Double-blind	14-week, double-blind treatment period	5-day inpatient treatment period (1-day up-titration with a 48-hour evaluation via video EEG in the last 2 days)	12-week evaluation	24-week treatment period (4 week up-titration plus 20 week evaluation periods)
Follow-up	Patients could either withdraw study drug over 6 weeks or enter a blinded conversion period leading to an open-label extension study	NA	6-week down-titration/ conversion period	NA
Outcomes				
Primary end point	Partial seizure frequency (all types) per week during the treatment period	Responder rate: % of patients with ≥ 50% reduction in average daily	Responder rate: ≥ 50% reduction from baseline in days per week with myoclonic seizures	• Mean % reduction from baseline in GTC seizure frequency/week

Detail	Partial onset seizures		Myoclonic seizures	GTC seizures
	Study N159 Glauser et al. (2006)[21]	Study N1009 Pina-Garza et al. (2009)[22]	Study N166 Noachtar et al. (2008)[23]	Study N1057 Berkovic et al. (2007)[24]
		partial onset seizure frequency		• Median % reduction from baseline in GTC seizure frequency/week; all seizures
Secondary and exploratory end points	• Responder rate • % reduction from baseline in partial seizure frequency • % reduction from baseline in partial seizure frequency by category • Absolute change from baseline in partial seizure frequency • Cumulative % of seizure-free patients from start of evaluation phase • Partial seizure frequency/week during the up-titration and evaluation periods	• Responder rate for all seizures • Absolute reduction in average daily seizure frequency for partial onset and all seizures • % reduction in average daily seizure frequency for partial onset, and all seizures	• Responder rate • Median % reduction from baseline in myoclonic seizure days/week and in all seizure days/week during treatment period (up-titration plus evaluation)	• Responder rate for GTC seizure frequency/ week • Freedom from GTC seizures and all seizure types
Notes				
Publications	Glauser et al. (2006) NCT00615615	Pina-Garza et al. (2009) Clinicaltrials.gov number unknown	Noachtar et al. (2008) NCT00150774	Berkovic et al. (2007) NCT00160550

AED: antiepileptic drug; b.i.d. = twice a day; CNS = central nervous system; EEG: electroencephalography; GTC: generalized tonic-clonic; IGE = idiopathic generalized epilepsy; JAE = juvenile absence epilepsy; JME = juvenile myoclonic epilepsy; LEV: levetiracetam; NA = not available; SE: status epilepticus.

Source: Berkovic et al. (2007),[24] Glauser et al. (2006),[21] Noachtar et al. (2008),[23] and Pina-Garza et al. (2009).[22]

Description of Studies

The 7 studies from Table 5 and Table 6 will be described in the following section.

Adults (Aged 16 Years to 70 Years)

Adequate and similarly designed well-controlled clinical trials conducted by UCB Pharma (studies N051, N132, and N138), taken together, provide substantial evidence of effectiveness of levetiracetam as adjunctive treatment for partial onset seizures in adults with epilepsy.

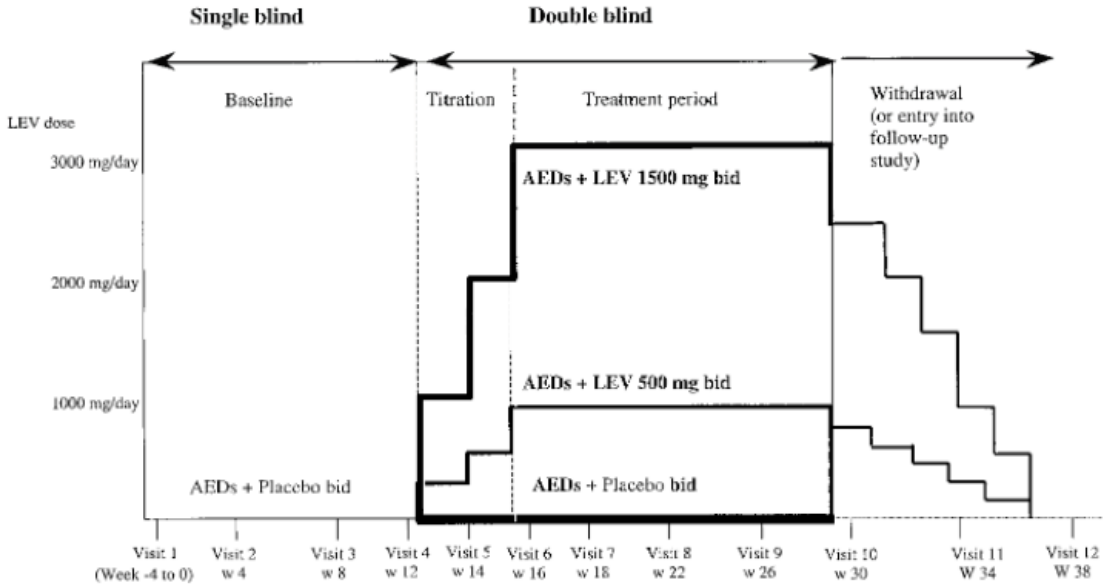
Study Design – All Studies (Study N051, Study N132, and Study N138)

All studies[18-20] consisted of a baseline observation and/or screening phase (4 weeks to 12 weeks), followed by an 8-week to 12-week up-titration phase in which levetiracetam was introduced alongside the patients' AEDs and increased, typically in 2-week intervals, until patients reached the pre-specified target dose. Patients were then maintained on levetiracetam treatment (8 to 14 weeks), after which patients were either withdrawn from

levetiracetam therapy slowly (down-titration phase) or entered into an open-label follow-on study. In Study N138 (Ben-Menachem et al.), once patients were titrated (4 weeks) they were evaluated for 12 weeks as add-on therapy (levetiracetam + AED). Those who demonstrated a response to treatment entered a 12-week levetiracetam monotherapy phase in which the patient was withdrawn from the concomitant AED. Study design respected criteria laid out in Clinical Investigations of Medicinal Products in the treatment of epileptic disorders.

- **Study objectives**
  - **Study N132 (Cereghino et al.):** To evaluate the efficacy and safety of 500 mg twice daily and 1,500 mg twice daily levetiracetam as adjunctive therapy for refractory partial seizures.
  - **Study N051 (Shorvon et al.):** To evaluate the efficacy and tolerability of levetiracetam (levetiracetam, Keppra) as add-on therapy in patients with refractory partial seizures.
  - **Study N138 (Ben-Menachem et al.):** To evaluate the efficacy and tolerability of levetiracetam monotherapy in selected patients with refractory partial seizures.
- **Population (total of 904 patients were randomized to the 3 studies)**
  - **Study N051 (Shorvon et al.):** patients with uncontrolled simple or complex partial seizures, or both, with or without secondary generalization.
  - **Study N132 (Cereghino et al.):** patients with uncontrolled partial seizures with or without becoming secondarily generalized for at least 2 years.
  - **Study N138 (Ben-Menachem et al.):** patients with clinically observed partial seizures for at least the year before study entry and who had at least 2 complex partial seizures per 4 weeks during baseline despite treatment with 1 AED.
- **Treatments**
  - **Study N132 (Cereghino et al.):** adjunctive therapy with placebo (n = 95), levetiracetam 1,000 mg/day (n = 98), or levetiracetam 3,000 mg/day (n = 101).

Figure 1: Study Design for Cereghino et al. Study

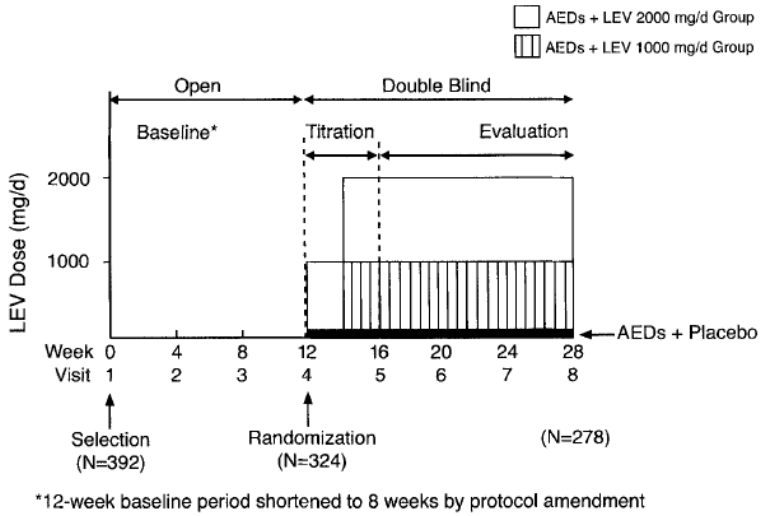


AED = antiepileptic drug; bid = twice a day; LEV = levetiracetam.

Source: Permission obtained from the publisher to use Figure 2 from Cereghino et al. (2000).[19]

- **Study N051 (Shorvon et al.):** levetiracetam (500 mg or 1,000 mg twice daily) was compared with placebo as add-on therapy in 324 patients with uncontrolled simple or complex partial seizures, or both, with or without secondary generalization.

Figure 2: Study Design for Shorvon et al. Study



AED = antiepileptic drug; LEV = levetiracetam.

Source: Permission obtained from the publisher to use Figure 1 from Shorvon et al. (2000).[18]

- **Study N138 (Ben-Menachem et al.):** Levetiracetam 1,500 mg twice daily was compared to placebo.

Figure 3: Study Design for Ben-Menachem et al. Study

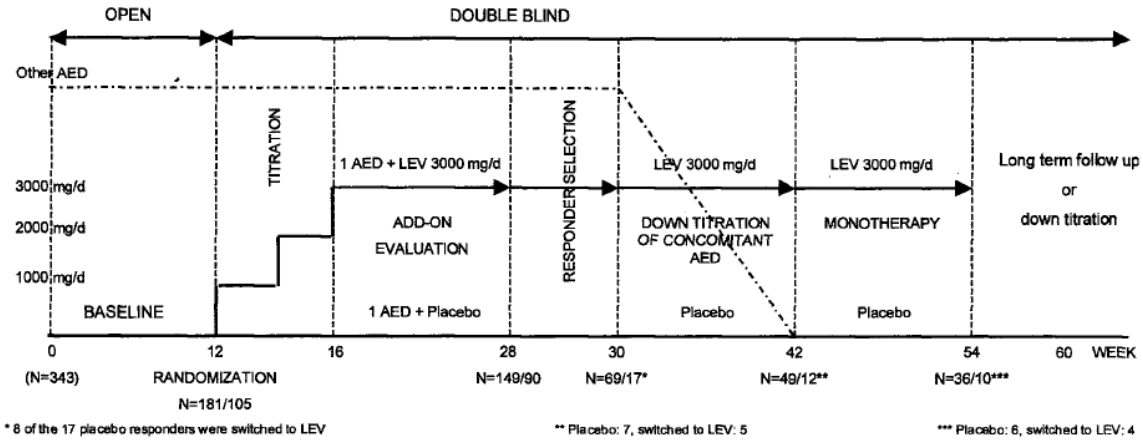


FIG. 1. Study design illustrating time line and components for each segment of the study.

AED = antiepileptic drug; LEV = levetiracetam.

Source: Permission obtained from the publisher to use Figure 1 from Ben-Menachem et al. 2000.[20]

Children (Aged 1 Month to < 4 Years)

To support the use of levetiracetam in this population, UCB Pharma submitted 1 pivotal safety and efficacy study in children as young as 1 month of age (Study N1009, Pina-Garza et al.[22]).

Study N1009 (Pina-Garza et al.)

Figure 4: Study Design for Pina-Garza et al. Study

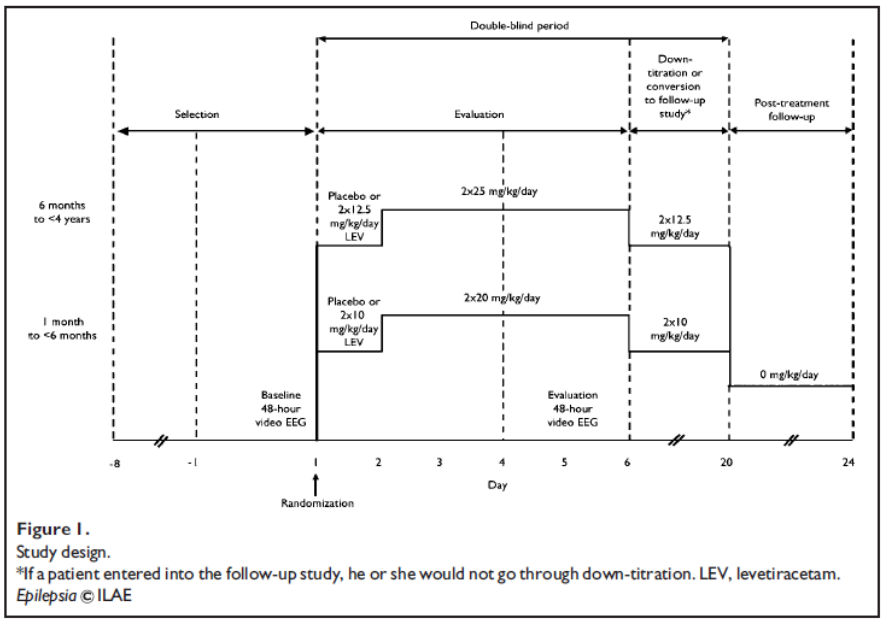


Figure 1.
Study design.
*If a patient entered into the follow-up study, he or she would not go through down-titration. LEV, levetiracetam.
Epilepsia © ILAE

EEG = electroencephalogram; LEV = levetiracetam.

Source: Permission obtained from the publisher to use Figure 1 from Pina-Garza et al. (2009). [22]

- **Study design:** A randomized, double-blind, multi-centre, placebo-controlled study with a 5-day inpatient treatment period (1-day up-titration; 48-hour evaluation via video electroencephalogram [EEG] in the last 2 days).
- **Objective:** To evaluate the efficacy and tolerability of adjunctive levetiracetam in very young children (aged 1 month to < 4 years) with partial onset seizures inadequately controlled with 1 or 2 AEDs.
- **Primary efficacy end point:** A 50% responder rate for partial onset seizures, defined as the percentage of subjects with a 50% or greater reduction in their average daily partial onset seizure frequency, as recorded on the evaluation 48 hour video EEG compared with the baseline 48-hour video EEG.
- **Population:** Pediatric patients aged 1 month to less than 4 years and weighing 4.0 kg or more were eligible if they had partial onset seizures inadequately controlled by 1 or 2 AEDs. There were no relevant differences in the abnormalities in the general medical history between treatment groups.
- **Treatment:** Concomitant AEDs were permitted.
  - levetiracetam (40 mg/kg per day [aged 1 month to < 6 months] and 50 mg/kg per day [aged > 6 months to < 4 years])
  - placebo.

Children (Aged 4 Years to 16 Years)

The primary basis for the demonstration of efficacy of levetiracetam in children for this indication by UCB Pharma was Study N159 (Glauser et al.[21]).

Study N159 (Glauser et al.)

- **Study design:** A North American, multi-centre, randomized, double-blind, placebo-controlled pivotal efficacy and safety study. The trial consisted of an 8-week baseline period followed by a 14-week double-blind treatment period. The treatment period was composed of a 4-week up-titration period and a 10-week evaluation period. At the conclusion of the double-blind treatment period, patients could either withdraw study drug over 6 weeks or enter a blinded conversion period leading to an open-label extension study.

Figure 5: Study Design for Glauser et al. Study

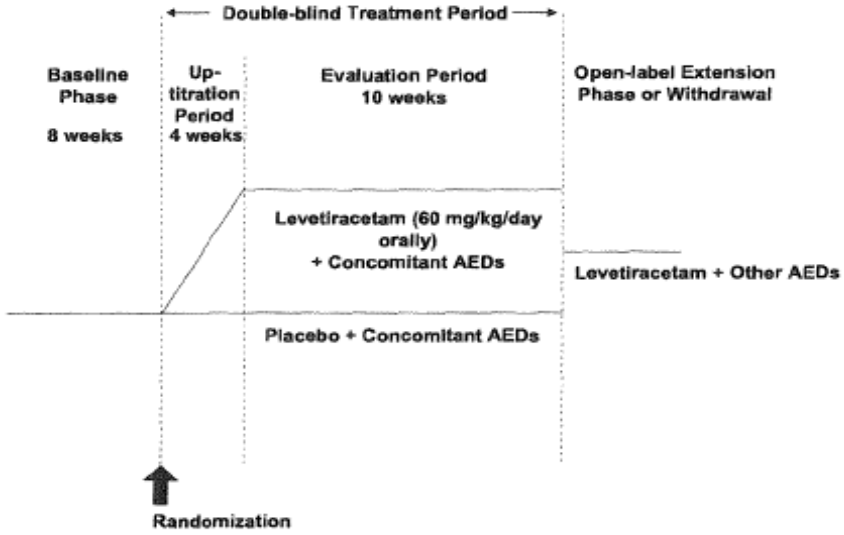


Figure 1. Trial design. AED = antiepileptic drug.

Source: Permission obtained from the publisher to use Figure 1 from Glauser et al. (2006).

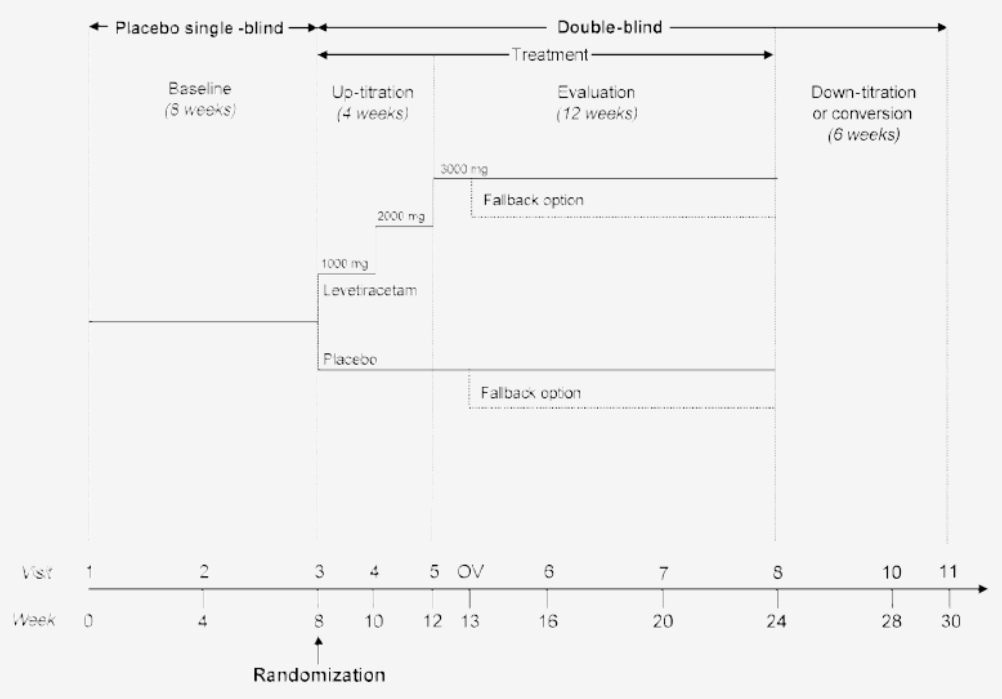
- **Objective:** To evaluate the efficacy and tolerability of levetiracetam as adjunctive therapy in children (aged 4 years to 16 years) with treatment-resistant partial onset seizures.
- **Primary efficacy end point:** Partial seizure frequency (including simple, complex, and secondarily generalized partial seizures) per week during the treatment period.
- **Population:** Pediatric patients aged 4 years to 16 years (N = 198) with partial onset seizures, with or without secondary generalization, uncontrolled by standard AEDs.
- **Treatments:** Concomitant AEDs were allowed.
  - Levetiracetam was initiated at 20 mg/kg per day administered as tablets in 2 divided doses. During the 4-week titration period, doses were adjusted in 20 mg/kg per day increments, at 2-week intervals, to the target dose of 60 mg/kg per day. If a patient could not tolerate 60 mg/kg per day, the dose could be reduced to 40 mg/kg per day.
  - Placebo.

Children and Adults (Aged 12 Years to 65 Years) – Myoclonic Seizures

Study N166 (Noachtar et al.)

- **Study design:** Double-blind, randomized, placebo-controlled study.
- **Objective:** To assess the efficacy, safety, and tolerability of levetiracetam 3,000 mg/day as adjunctive therapy for idiopathic generalized epilepsy in patients with myoclonic seizures that were not fully controlled despite treatment with 1 AED.
- **Primary efficacy end point:** A 50% or greater reduction in myoclonic seizure days per week (responder rate) during the treatment period (up-titration and evaluation) compared to baseline.
- Population: Patients (aged 12 years to 65 years) with refractory JME and juvenile absence epilepsy, who experienced 1 myoclonic seizure or more every 8 days or more during an 8-week baseline period. A higher proportion of subjects were female. Subject weight and body mass index were similar, with no noted differences between treatment groups.

Figure 6: Study Design for Noachtar et al. Study



OV = optional visit.

Source: Permission obtained from the publisher to use Figure 1 from Noachtar S et al. (2008).[23]

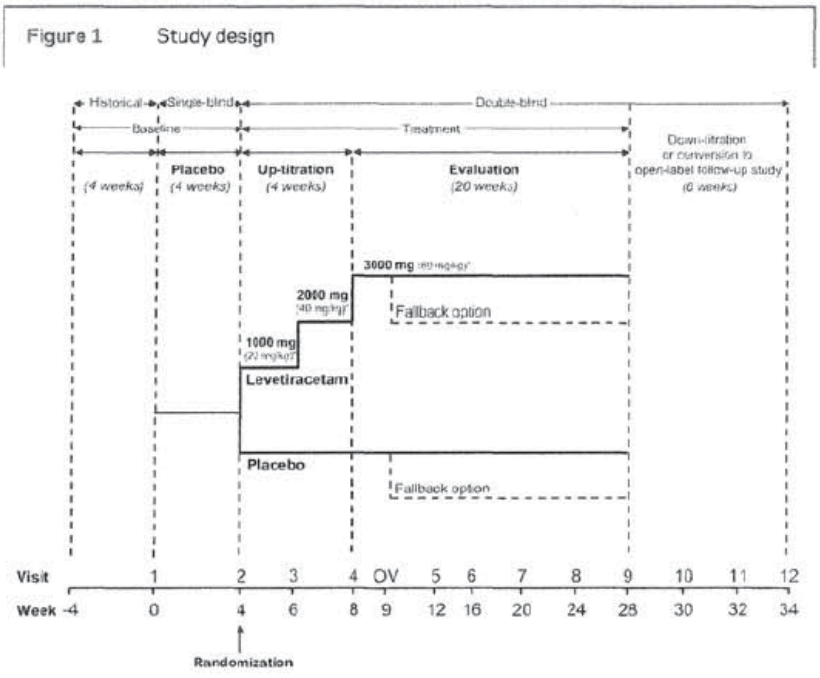
- **Treatment:** One concomitant AED was to be taken with the study treatment at a stable dose.
  - adjunctive levetiracetam 500 mg twice daily to start, increased to 2,000 and 3,000 mg/day of levetiracetam at 2-week intervals during an up-titration period
  - placebo.

Children and Adults (Aged 4 Years to 65 Years) – Generalized Tonic-Clonic Seizures

Study N1057 (Berkovic et al.)

- **Study design:** A double-blind, randomized, placebo-controlled study. Following a 4-week historical baseline period, patients entered a prospective 4-week, single-blind, placebo baseline period. The treatment was 20 weeks.
- **Objective:** Efficacy and tolerability of adjunctive levetiracetam treatment in adults and children with intractable childhood epilepsy and generalized tonic-clonic seizures that were uncontrolled despite treatment with 1 or 2 concomitant AEDs.
- **Primary efficacy end point:** Mean percent reduction from baseline in generalized tonic-clonic seizure frequency per week.
- **Population:** Patients (aged 4 years to 65 years) with a body weight of 20 kg or higher and suffering from refractory PGTC seizures, who experienced 3 or more generalized tonic-clonic seizures and received 1 to 2 AEDs, during an 8-week baseline period. The presence of other seizure types (absence, clonic, tonic, and myoclonic seizures) was well balanced between treatment groups.
- **Treatment:** All patients took another concomitant AED.
  - adjunctive levetiracetam (or placebo) was initiated over 4 weeks to a maintenance dose of 3,000 mg/day (60 mg/kg per day in pediatric patients < 16 years and < 50 kg) for 20 weeks; in patients not tolerating levetiracetam, dose was reduced to 2,000 mg/day or 40 mg/kg per day
  - placebo.

Figure 7: Study Design for Berkovic et al. Study



OV = optional visit.

Source: Permission obtained from the publisher to use Figure 1 from Berkovic et al. (2007).[24]

Populations

Inclusion and Exclusion Criteria

Generally, the patients had to have a clinically diagnosed epilepsy syndrome and to be stable on an AED for a certain period of time before joining the clinical trial. Patients were generally allowed to be on 1 or more concomitant medications, except for some publications that would not allow certain medications or would limit the concomitant medications to 1 or 2.

The patients were excluded if they had other neurologic or epileptic issues, other comorbidities that could impact the results, if they participated in another clinical trial previously, or if they had allergies to pyrrolidine derivatives or other medications. In some studies patients that had a history of status epilepticus or that had a ketogenic diet were excluded.

Adults (Aged 16 Years to 70 Years)

The following describes the inclusion and exclusion criteria for Study N051 (Shorvon et al.), Study N132 (Cereghino et al.), and Study N138 (Ben-Menachem et al.).

- **Inclusion:** Eligible patients were within the age range of 16 years to 70 years with a history of partial seizures within the last 1 year to 2 years, with or without secondarily generalization. The inclusion criteria stipulated a baseline seizure frequency of at least 1 partial onset seizure per week for Study N051 (Shorvon et al.) and Study N132 (Cereghino et al.), whereas Study N138 (Ben-Menachem et al.) required patients with at least 1 complex partial seizure every 2 weeks.
- **Exclusion:** Generally, all other chronic comorbidities besides epilepsy (neurologic or other) and abnormal blood results were exclusion criteria. Study N051 (Shorvon et al.) had no mention of exclusion due to prior participation in a clinical trial, but Study N132 and Study N138 did. Only Study N138 excluded patients due to history of status epilepticus.

Children (Aged 1 Month to < 4 Years)

Study N1009 (Pina-Garza et al.)

- **Inclusion:** Patients were maintained on a stable regimen of 1 or 2 concomitant AEDs for the selection and evaluation periods. During the 2-week period prior to the baseline visit, the addition or discontinuation of AEDs was not permitted but minor adjustments to the current AED dose, at the investigators' discretion, were allowed. Vagus nerve stimulation implanted for at least 6 months prior to the baseline visit, and with stable settings for at least 2 months prior to that visit, was allowed and considered as 1 of the 2 AEDs.
- **Exclusion:** The main exclusion criteria included a diagnosis of a treatable seizure etiology, for example metabolic, toxic, and infectious disorders, or febrile seizures; status epilepticus that required hospitalization during the month before the baseline visit; current diagnosis of Lennox-Gastaut syndrome; epilepsy secondary to a progressive cerebral or neurodegenerative disease; a history of, or the presence of, pseudoseizures; previous use of levetiracetam; and clinically significant abnormal laboratory value or medical condition.

Children (Aged 4 Years to 16 Years)

Study N159 (Glauser et al.)

- Inclusion: Partial seizures (including the subtypes of simple, complex, and partial seizures evolving to secondarily generalized seizures) that at the time of enrolment were inadequately controlled with 1 or 2 concomitant AEDs. The diagnosis of epilepsy had to

be made at least 6 months before the screening visit. To qualify for randomization, patients were required to have 4 or more partial seizures during the 4 weeks preceding the screening visit and to have 4 or more partial seizures during each 4-week interval of the 8-week baseline period. AED dosages had to remain unchanged during the study's baseline and treatment periods (including the up-titration and evaluation periods). Intermittent benzodiazepines (≤ 1 administration per week) were allowed; routine benzodiazepine use was allowed as 1 of the 2 AEDs. Vagal nerve stimulation implanted more than 6 months before the screening visit, and with stable settings for the 2 months preceding that visit, was allowed and considered 1 of the 2 AEDs.

- **Exclusion**: Pregnant or nursing females or those trying to conceive were excluded. Patients with evidence or history of any of the following were excluded: a treatable seizure etiology, seizures too close together, or pseudoseizures; epilepsy secondary to a progressive cerebral disease or any other progressively neurodegenerative disease; status epilepticus that required hospitalization during the 3 months before the screening visit; current diagnosis of Lennox-Gastaut syndrome; a cardiovascular, respiratory, hepatic, renal, gastrointestinal, hematologic, oncologic, psychiatric, or progressive neurologic disorder likely to have an impact on the outcome of the trial; current or past allergy to pyrrolidone derivatives or a history of multiple drug allergies; any medication (other than a concomitant AED) acting on the central nervous system that had not been on a stable regimen for more than 1 month before the screening visit; felbamate use for less than 18 months before the screening visit; use of any investigational drug or device during the 30 days before the screening visit; participation in any previous levetiracetam study; or use of a ketogenic diet within 30 days before the screening visit.

Children and Adults (Aged 4 Years to 65 Years)

Children and Adults (Aged 12 Years to 65 Years) – Myoclonic Seizures

Study N166 (Noachtar et al.)

- **Inclusion:** Patients with myoclonic seizures on 8 or more days during the study baseline period and who were receiving a stable dose of 1 AED for 4 or more weeks before study entry were included. Although the diagnosis of the syndrome was not standardized among the different recruiting centres, eligible patients were selected by the investigators, certified neurologists, and epileptologists, based on clinical and EEG features consistent with idiopathic generalized epilepsy (EEG taken during the baseline period or within 1 year of study entry), absence of evidence of brain lesions (CT scan or MRI), and diagnosis of JME, juvenile absence epilepsy, or epilepsy with generalized tonic-clonic seizures on awakening, in accordance with the ILAE classification of epileptic syndromes. Females of childbearing potential were eligible if they used a medically accepted contraceptive method.
- **Exclusion:** Patient exclusion criteria included nonepileptic seizures within the previous year; signs suggestive of a progressive brain lesion; history of partial onset seizures; status epilepticus within the previous 3 months; previous or current treatment with levetiracetam; current use of vigabatrin or tiagabine; or current use of felbamate with less than 18 months exposure.

Children and Adults (Aged 4 Years to 65 Years) – Generalized Tonic-Clonic Seizures

Study N1057 (Berkovic et al.)

- **Inclusion:** Patients aged 4 years to 65 years (weight ≥ 20 kg) with a confirmed electroclinical diagnosis consistent with ICE, who were experiencing generalized tonic-clonic seizures despite treatment with 1 or 2 AEDs were included. There was no standardization for the syndrome diagnosis between the different recruiting centres. Where possible, idiopathic generalized epilepsy subsyndromes were identified by the investigators and patients with a diagnosis of JME, childhood absence epilepsy, juvenile

absence epilepsy, or epilepsy with generalized tonic-clonic seizures on awakening were included. Patients had to have experienced 3 or more generalized tonic-clonic seizures during the 8-week combined baseline period, with 1 or more seizures during historical (4-week) and prospective (4-week) baseline periods and CT or MRI done in the last 5 years did not show a progressive brain lesion. Patients also had to have been receiving a stable dose of 1 or 2 AEDs during the 8-week combined baseline period. Vagal nerve stimulation within 4 weeks of study visit 1 was counted as 1 of the patient's concomitant AEDs.

- **Exclusion:** The main exclusion criteria were partial onset seizures, including secondarily GTC seizures, pseudoseizures within the last year, seizures occurring only in clustered patterns, and a history of status epilepticus while taking AEDs within the 3 months before study visit 1. Patients with partial seizures in addition to documented generalized seizures as part of an ICE syndrome, were not excluded.

Baseline Characteristics

Patient demographic characteristics were similar across all studies.

Adults (Aged 16 Years to 70 Years)

- **Study N051 (Shorvon et al.):** Demographic characteristics were comparable between treatment groups and 99% of patients were White. Across all treatment groups, the mean duration of epilepsy was 24 years, and the mean age of epilepsy onset was 14 years. For more than half of the patients (57%) the cause of epilepsy was cryptogenic. Baseline seizure frequency was comparable between groups. The number of AEDs taken by patients at baseline and throughout the study was similar among treatment groups. Most patients' conditions had been stabilized on carbamazepine (72%), phenytoin (22%), or valproate (21%). Among newer agents, the most frequently prescribed were vigabatrin (18%), lamotrigine (12%), and gabapentin (2%).
- **Study N132 (Cereghino et al.):** No significant differences in demographics were noted between groups. Reasons for discontinuation were evenly distributed among treatment groups, except in the "other" category, where all patients were in the levetiracetam 1,000 mg/day group (3 failure to return, 1 lack of efficacy).
- **Study N138 (Ben-Menachem et al.):** Baseline demographic and disease characteristics of the 2 treatment groups were comparable with respect to age, sex, race, duration of epilepsy, and age at epilepsy onset. The proportion of seizure types was equivalent between the 2 treatment groups. There were no patients who had primarily generalized seizures or unclassifiable seizures during the baseline period. The most frequently prescribed AEDs were carbamazepine (74%), lamotrigine (9%), valproate (8%), and phenytoin (6%).

Children (Aged 1 Month to 16 Years)

- **Study N159 (Glauser et al.):** The treatment groups were well matched. Males represented just over 50% of the patient population. The publication did not list the race of the participants.
- **Study N1009 (Pina-Garza et al.):** The treatment groups were well matched in terms of age, gender, weight, seizure type, and age at onset of epilepsy. The majority of patients (90%) on levetiracetam were White, compared with 69.6% on placebo. The baseline median daily partial onset seizure frequency was higher in the levetiracetam group (15.2) compared with placebo (6.8). The majority of patients were taking 2 concomitant AEDs (levetiracetam 71.7%; placebo 69.6%), whereas a smaller proportion took 1 AED (levetiracetam = 21.7%; placebo = 21.4%).

Children and Adults (Aged 4 Years to 65 Years)

Children and Adults (Aged 12 Years to 65 Years) – Myoclonic Seizures

- **Study N166 (Noachtar et al.):** The majority of subjects were White (approximately 75%), with a small representation of Hispanic subjects. A higher proportion of subjects were female. Subject weight and body mass index were similar, with no noted differences between treatment groups.

Children and Adults (Aged 4 Years to 65 Years) – Generalized Tonic-Clonic Seizures

- **Study N1057 (Berkovic et al.):** There was a noted higher mean age in the placebo group compared with the levetiracetam group. In this study, 10.4% of patients were under the age of 16 years. A higher proportion of subjects were female. Subject weight and body mass index were similar, with no noted differences between treatment group within each study.

Table 7: ITT Analysis – Adults With Partial Onset Seizures (Adapted From Table 17 in 2.7.4 Summary of Clinical Safety)[27]

Demographic characteristics	Study N051[a]			Study N132[b]			Study N138	
	PBO N = 112	LEV 1,000 mg N = 106	LEV 2,000 mg N = 106	PBO N = 95	LEV 1,000 mg N = 98	LEV 3,000 mg N = 101	PBO N = 105[c]	LEV 3,000 mg N = 181
Age (years)								
Mean (SD)	37 (12)	36 (10)	37 (12)	38 (11)	38 (11)	38 (11)	36 (12)	37 (12)
Range	16 to 69	16 to 68	14 to 65	20 to 65	16 to 70	16 to 66	17 to 69	17 to 70
Gender, n (%)								
Male	55 (49)	51 (48)	51 (48)	50 (53)	62 (63)	66 (65)	51 (49)	87 (48)
Female	57 (51)	55 (52)	55 (52)	45 (47)	36 (37)	35 (35)	54 (51)	94 (52)
Race, n (%)								
White	109 (97)	106 (100)	106 (100)	81 (85)	82 (84)	88 (87)	105 (100)	181 (100)
African American	2 (2)	0	0	7 (7)	10 (10)	9 (9)	0	0
Other	1 (1)	0	0	7 (7)	6 (6)	4 (4)	0	0
Age of seizure onset (year)								
Mean (SD)	14.2 (10.9)	13.1 (11.5)	13.7 (10.9)	NR	NR	NR	18 (13)	18 (14)
Duration of epilepsy (years)								
Mean (SD)	23.2 (11.0)	3.8 (12.3)	23.6 (13.3)	NR	NR	NR	19 (12)	19 (11)
Median (range)	22.4 (2 to 52)	22.6 (1 to 55)	22.9 (2 to 60)	24	22	23	17	17
Cause, n (%)								
Cryptogenic (unknown[d])	64 (57.1)	59 (55.7)	60 (56.6)	NR	NR	NR	50.5%	59.1%
Baseline seizure frequency (n per week)								
Median (range)	2.50 (1.27 to 4.94)	2.82 (1.75 to 4.39)	2.58 (1.50 to 6.25)	1.77[e]	2.53[e]	2.08[e]	1.75	1.69
Baseline seizure frequency and type								
Partial onset								
Mean	5.39	5.51	6.88	5.05	6.87	5.50	5.83	4.49

Demographic characteristics	Study N051[a]			Study N132[b]			Study N138	
	PBO N = 112	LEV 1,000 mg N = 106	LEV 2,000 mg N = 106	PBO N = 95	LEV 1,000 mg N = 98	LEV 3,000 mg N = 101	PBO N = 105[c]	LEV 3,000 mg N = 181
n (%)	40 (36)	31 (29)	30 (28)					
Simple partial								
Mean	2.02	2.19	2.16	4.26	5.68	5.84	0.99	1.43
n (%)	93 (83)	84 (79)	93 (88)	NR	NR	NR	NR	NR
Complex partial								
Mean	3.21	2.91	4.48	2.76	3.66	2.53	4.73	2.93
n (%)	93 (83)	84 (79)	93 (88)	NR	NR	NR	NR	NR
Secondarily generalized								
Mean	0.16	0.33	0.26	0.13	0.59	0.35	0.21	0.13
n (%)	26 (23)	28 (26)	29 (27)	NR	NR	NR	NR	NR
Other, n (%)	8 (7)	4 (4)	10 (9)	NR	NR	NR	NR	NR
Concomitant AEDs n (%)								
Carbamazepine	79 (71)	75 (71)	80 (75)	59 (62)	52 (53)	56 (55)	80 (76)	132 (73)
Clobazam	9 (8)	10 (9)	12 (11)	3 (3)	1 (1)	2 (2)		
Clonazepam	4 (4)	7 (7)	3 (3)	NR[f]	NR	NR	1 (1)	0 (0.0)
Diazepam	7 (6)	6 (6)	10 (9)	24 (25)	35 (35)	24 (24)	5 (5)	2 (1)
Gabapentin				4 (4.2)	3 (3.1)	5 (5.0)	NR	NR
Lamotrigine	14 (13)	13 (12)	11 (10)	NR	NR	NR	10 (10)	15 (8)
Oxcarbazepine	NR	NR	NR	NR	NR	NR	0 (0)	3 (2)
Phenobarbital	14 (13)	11 (10)	8 (8)	7 (7)	9 (9)	10 (10)	NR	NR
Phenytoin	30 (27)	21 (20)	21 (20)	29 (30)	37 (38)	36 (36)	9 (9)	8 (4)
Primidone	7 (6)	7 (7)	6 (6)	9 (9)	2 (2)	9 (9)	NR	NR
Valproate	21 (19)	25 (24)	21 (20)	28 (29)	24 (24)	26(26)	4 (4)	20 (11)
Vigabatrin	NR	NR	NR	NR	NR	NR	2 (2)	3 (2)

Demographic characteristics	Study N051[a]			Study N132[b]			Study N138	
	PBO N = 112	LEV 1,000 mg N = 106	LEV 2,000 mg N = 106	PBO N = 95	LEV 1,000 mg N = 98	LEV 3,000 mg N = 101	PBO N = 105[c]	LEV 3,000 mg N = 181
Other[f]	NR	NR	NR	7 (7.4)	5 (5.1)	8 (7.9)	NR	NR

AED = antiepileptic drug; ITT = intention to treat; LEV = levetiracetam; NA = not available; PBO = placebo; SD = standard deviation.

[a] Total patient numbers per AED were derived from the addition of the total number of patients per treatment group (LEV and PBO), as per Table 10 in the Keppra FDA Clinical Review NDA 21-035. Percentages were then calculated based on the total across all treatment groups ÷ N × 100.

[b] Total patient numbers per AED were derived from the addition of the total number of patients per treatment group (LEV and PBO), as per Table 22 in the Keppra FDA Clinical Review, NDA 21-035. Percentages were then calculated based on the total across all treatment groups ÷ N × 100.

[c] For the demographic characteristics (i.e., age, gender, race, median years with epilepsy), the number of patients in the control group was 95: For AEDs and seizure type, the total number of placebo-treated patients was 105. Note that in the published article Ben-Menachem et al. (2000), the ITT population for the placebo group was 105, whereas in the FDA review (Keppra FDA Clinical Review, NDA-21-035), the ITT placebo group population was recorded as N = 95.

[d] Subset of ITT patients who had adequate (non-missing and properly completed) at both baseline and following randomization; placebo, N = 36; LEV 2,000 mg, N=34, and LEV 4,000 mg, N = 36.

[e] Seizure frequency = (7 × total number of seizures during baseline) ÷ length of baseline. Seizure data are log-transformed.

[f] Methosuximide, acetaxolamide, lorazepam, tiagabine, clorazepate dipotassium, diazepam.

Table 8: ITT Analysis – Partial Onset in Children (Aged 1 Month to 16 Years) and Generalized Seizures in Children and Adults (Aged 4 Years to 65 Years)

Demographic characteristics	Partial onset				Myoclonic seizures		GTCS	
	Study N159 Glauser (2006)		Study N1009 Pina-Garza (2009)		Study N166 Noachtar et al. (2008)		Study N1057 Berkovic et al. (2007)	
	LEV (N = 101)	PBO (N = 97)	LEV (N = 60)	PBO (N = 56)	LEV (N = 61)	PBO (N = 60)	LEV (N = 80)	PBO (N = 84)
Age (years)								
Mean (SD)	10.2 (3.2)	9.8 (3.4)	23.40 (13.43) (months)	23.15 (11.90) (months)	25.0 (7.4)	26.8 (9.5)	26.9 (11.2)	30.6 (12.1)
Median (range)	10.4 (4.1 to 17.0)	9.7 (3.3 to 17.2)	21.00 (months)	22.00 (months)	13.8 to 50.7	14.2 to 52.4	NA	NA
Age range, n (%)								
1 month to < 6 months	NA	NA	4 (6.7)	4 (7.1)	NA	NA	NA	NA
6 months to < 12 months	NA	NA	8 (13.3)	7 (12.5)	NA	NA	NA	NA
12 months to < 24 months	NA	NA	20 (33.3)	18 (32.1)	NA	NA	NA	NA

Demographic characteristics	Partial onset				Myoclonic seizures		GTCS	
	Study N159 Glauser (2006)		Study N1009 Pina-Garza (2009)		Study N166 Noachtar et al. (2008)		Study N1057 Berkovic et al. (2007)	
	LEV (N = 101)	PBO (N = 97)	LEV (N = 60)	PBO (N = 56)	LEV (N = 61)	PBO (N = 60)	LEV (N = 80)	PBO (N = 84)
24 months to < 48 months	NA	NA	28 (46.7)	25 (48.2)	NA	NA	NA	NA
Weight								
Mean (SD)	36.6 (16.9)	37.1 (17.2)	11.2 (3.6)	11.7 (4.1)	69.2 (15.0)	69.4 (14.7)	69.0 (21.1)	72.5 (20.4)
Median (range)	34.0 (12.5 to 86.9)	32.8 (11.8 to 83.0)	NA	NA	NA	NA	NA	NA
Gender, n (%)								
Male	54 (53.5)	46 (47.4)	30 (50.0)	27 (48.2)	22 (36.1)	22 (36.7)	34 (42.5)	39 (46.4)
Female	47 (46.5)	51 (52.6)	30 (50.0)	29 (55.5)	39 (63.9)	38 (63.3)	46 (57.5)	45 (53.6)
Race, n (%)								
White	NA	NA	54 (90.0)	39 (69.6)	46 (75.4)	47 (78.3)	57 (71.3)	64 (76.2)
Hispanic	NA	NA	NA	NA	15 (24.6)	10 (16.7)	NA	NA
African American	NA	NA	0	6 (10.7)	NA	NA	NA	NA
Other/multi-racial	NA	NA	2 (3.3)	8 (14.3)	0 (0.0)	3 (5.0)	23 (28.7)[a]	20 (23.8)
Age of seizure onset (years)								
Mean (SD)	2.9 (2.9)	3.1 (3.1)[a]	5.8 (8.4)	6.8 (8.3)	13.1(4.3)[a]	12.7 (5.4)	10.6 (6.1)	12.6 (6.2)
Median (range)	1.8 (0.0 to 12.5)	NA	NA	NA	NA	NA	NA	NA
Duration of epilepsy (years)								
Mean (SD)	7.4 (3.7)	6.8 (3.5)	NA	NA	11.8 (8.5)[a]	14.1 (11.3)	16.3 (11.6)	18.0 (13.0)
Median (range)	6.7 (1.1 to 15.1)	6.7 (0.7 to 16.0)	NA	NA	NA	NA	NA	NA
Concomitant AEDs, n (%)								
1	31 (30.7)	36 (37.1)	13 (21.7)	12 (21.4)	NA	NA	NA	NA
2	61 (60.4)	54 (55.7)	43 (71.7)	39 (69.6)	NA	NA	NA	NA
> 2	9 (8.9)	7 (7.2)	4 (6.7)	5 (8.9)	NA	NA	NA	NA
≥ 3	NA	NA	NA	NA	NA	NA	NA	NA

Demographic characteristics	Partial onset				Myoclonic seizures		GTCS	
	Study N159 Glauser (2006)		Study N1009 Pina-Garza (2009)		Study N166 Noachtar et al. (2008)		Study N1057 Berkovic et al. (2007)	
	LEV (N = 101)	PBO (N = 97)	LEV (N = 60)	PBO (N = 56)	LEV (N = 61)	PBO (N = 60)	LEV (N = 80)	PBO (N = 84)
Concomitant AEDs, n (%)								
Oxcarbazepine	12 (12.9)	10 (10.3)	14 (23.3)	8 (14.3)	1 (1.6)	2 (3.3)	NA	NA
Carbamazepine	35 (34.7)	37 (38.1)	5 (8.3)	13 (23.2)	2 (3.3)	2 (3.3)	17 (21.5)[b]	14 (16.7)[b]
Lamotrigine	23 (22.8)	20 (20.6)	NA	NA	15 (24.6)	17 (28.3)	22 (27.8)[b]	23 (27.4)
Valproic acid	26 (25.7)	28 (28.9)	25 (41.7)	21 (37.5)	37 (60.7)	33 (55.0)	42 (53.2)[b]	44 (52.4)
Topiramate	29 (28.7)	31 (32.0)	21 (35.0)	16 (28.6)	3 (4.9)	3 (5.0)	8 (9.5)	19 (11.6)
Phenobarbital	NA	NA	22 (36.7)	18 (32.1)	4 (6.6)	4 (6.7)	NA	NA
Clobazam	NA	NA	7 (11.7)	3 (5.4)	NA	NA	NA	NA
Clonazepam	NA	NA	3 (5.0)	9 (16.1)	1 (1.6)	2 (3.3)	NA	NA
Vigabatrin	NA	NA	8 (13.3)	11 (19.6)	NA	NA	NA	NA
Phenytoin	NA	NA	NA	NA	2 (3.3)	1 (1.7)	6 (7.6)[b]	11 (13.1)
Gabapentin	NA	NA	NA	NA	1 (1.6)	0 (0.0)	NA	NA
Ethosuximide	NA	NA	NA	NA	0 (0.0)	1 (1.7)	NA	NA

AED = antiepileptic drug; GTCS = generalized tonic-clonic seizure; ITT = intention to treat; LEV = levetiracetam; NA = not available; PBO = placebo; SD = standard deviation.

Note: Entries marked by NA indicate fields for which information was not available from study articles or foreign reviewer reports.

[a] Calculated percentages based on number of patients provided in study article. Numbers were rounded to nearest whole number by 1 decimal places.

[b] For Study N1057, the percentage was based on 79 patients in the LEV group, since 1 patient was lost to follow-up after randomization. Overall percentages were based on a total patient population of 165.

Source: Adapted from Tables 18, 20, 24, 25, 26 in 2.7.4 Summary of clinical safety[27] and from individual publication [Pina-Garza 2009]).[22]

Interventions

In all studies, levetiracetam was administered as a tablet or oral solution and was compared to placebo. No study compared levetiracetam to another AED.

Levetiracetam was studied as an adjunctive treatment, hence another stable AED was always permitted. A few publications required that the other AED be stable for some time before entering the study.

Table 9: Intervention in Adults (Aged 16 Years to 70 Years)

Drug regimen	Study N051 Shorvon (2000)	Study N132 Cereghino (2000)	Study N138 Ben-Menachem (2000)
Interventions (dose, frequency)	**Oral tablets** **Treatment** • LEV 1,000 mg/day (500 mg b.i.d.) • LEV 2,000 mg/day (1,000 mg b.i.d.)	**Oral tablets** given in 2 divided doses before meals. **Treatment:** • LEV 1,000 mg/day • LEV 3,000 mg/day	**Oral tablets** **Treatments:** • Oral LEV 1,500 mg b.i.d. • Patients who could not tolerate the target LEV dose could fall back to a dose of 2,000 mg/day (40 mg/kg per day)
Comparator and description	Placebo **Description:** NA as all study medications (LEV and placebo) used in this study were supplied and packaged by UCB Pharma	Placebo **Description:** identical white, film-coated, scored tablets containing either 166.5 mg LEV (batch numbers 75 and 76), 500 mg LEV (batch numbers 70, 72, 74, and 78), or placebo (batch numbers 73P and 77P); unbroken tablets were equal in taste; tablets were not to be broken; LEV tablets and matching placebo were supplied by UCB S.A. Pharma Sector (Braine-l'Alleud, Belgium)	Placebo NA
Titration schedule	**Schedule:** twice daily increments of 500 mg at 2-week intervals until patients were stabilized 1,000 mg group received placebo for 2 weeks before initiation of active drug	**Schedule:** escalated at 2-week intervals during the 4-week titration phase: 333 mg/day for 2 weeks, then 666 mg/day for 2 weeks, and 1,000 mg/day started on the first visit of the observation period, or 1,000 mg/day, 2,000 mg/day, then 3,000 mg/day	Titration period: 4 weeks **Schedule:** study medication was titrated upward every 2 weeks from 500 mg twice daily to the target dosage of 1,500 mg twice daily (up-titration period)
Concomitant medications	Patients were allowed to intake concomitant medication Total number of concomitant AEDs during study in all groups: 1 (n = 60; 19%), 2 (n = 247; 76%), ≥ 3 (n = 17; 5%)	Patients continued on concomitant AEDs at the same dosage throughout the trial. Substitutions in concomitant AEDs were not allowed. If a clinical adverse event was considered associated with a rise in concomitant AED blood level, the investigator was permitted to modify that drug's dosage. Other drugs affecting the CNS were to be avoided.	Included participants were eligible if they had uncontrolled seizures despite treatment with 1 or 2 concomitant AEDs

AED = antiepileptic drug; b.i.d. = twice a day; CNS = central nervous system; LEV = levetiracetam; NA = not available; UCB = Union Chimique Belge.

Source: Ben-Menachem et al. (2000), Cereghino et al. (2000), Shorvon et al. (2000).

Table 10: Intervention in Children (Aged 1 Month to 16 Years) and Children Plus Adults (Aged 4 Years to 65 Years)

Drug regimen	Partial onset		Myoclonic seizures	GTCS
	Study N159 Glauser et al. (2006)	Study N1009 Pina-Garza et al. (2009)	Study N166 Noachtar et al. (2008)	Study N1057 Berkovic et al. (2007)
Interventions (dose, frequency)	**Oral tablets** LEV initiated at 20 mg/kg per day b.i.d. (approximately 12 hours apart) Target dose of 60 mg/kg per day	**10% Oral solution (100 mg/mL)** **Aged 1 month to < 6 months:** LEV started at 20 mg/kg per day on day 1, maintained at 40 mg/kg per day **Aged 6 months to < 4 years:** LEV started at 25 mg/kg per day on day 1, maintained at 50 mg/kg per day	**Oral tablet** Maintenance dose of LEV 3,000 mg/day	**Oral tablet** **Adults:** 3,000 mg/day **Children:** 60 mg/kg per day
Comparator and description	Placebo Blinding was maintained through the use of matching LEV and placebo tablets of identical appearance for oral administration; these tablets were packaged in blister cards to be dispensed to the patient.	Placebo Blinding was maintained through the use of matching grape-flavoured oral solutions of LEV and placebo.	Placebo Identical-looking study medication (tablets of 500 mg LEV or placebo) was administered as a twice-daily regimen.	Placebo During the single-blind, placebo baseline period the patients received the same blisters, containing the same number of tablets of identical appearance during the double-blind period.
Titration schedule	4 weeks titration Initial dose of 20 mg/kg per day, increasing every 2 weeks to a final target dose of 60 mg/kg per day If patient could not tolerate 60 mg/kg per day, the dose could be reduced to 40 mg/kg per day and maintained at that dose for the remainder of the evaluation period Patients exited the trial if they could not tolerate 40 mg/kg per day	1-day up-titration 1 month to < 6 months: initiated at 20 mg/kg per day and titrated to 40 mg/kg per day 6 months to < 4 years: initiated at 25 mg/kg per day and titrated to 50 mg/kg per day.	4-week up-titration period Treatment was initiated with 2 tablets/day (LEV 1,000 mg/day), increasing at 2-week intervals to 4 tablets/day (LEV 2,000 mg/day) and then 6 tablets/day (LEV 3,000 mg/day) A single fall-back option to 2,000 mg/day during the first week	4-week up-titration
Concomitant medications	Concomitant AEDs permitted	Patients were maintained on a stable regimen of 1 or 2 concomitant AEDs. During the 2-week period prior to the baseline visit,	One concomitant AED was to be taken with the study treatment at a stable dose (unless	All patients in the placebo group and 78 patients (98.7%) in the LEV group took ≥ 1 concomitant AED

Drug regimen	Partial onset		Myoclonic seizures	GTCS
	Study N159 Glauser et al. (2006)	Study N1009 Pina-Garza et al. (2009)	Study N166 Noachtar et al. (2008)	Study N1057 Berkovic et al. (2007)
		the addition or discontinuation of AEDs was not permitted but minor adjustments to the current AED dose, at the investigators' discretion, were allowed.	modified for safety reasons).	during the study treatment period

AED = antiepileptic drug; b.i.d. = twice a day; GTCS = generalized tonic-clonic seizure; LEV = levetiracetam.

Source: Berkovic et al. (2007),[24] Glauser et al. (2006),[21] Noachtar et al. (2008),[23] Pina-Garza et al. (2009).[22]

Outcomes

Quality of Life in Epilepsy questionnaire (QoLIE-31-P): This scale is composed of 30 items grouped into 7 subscales: seizure worry, overall quality of life, emotional well-being, energy/fatigue, cognitive functioning, medication effects, and social function, and 1 health status item. Additionally, the QoLIE-31-P includes items assessing the degree of distress associated with each subscale. Each subscale and the total score range from 0 to 100, with higher scores indicating better function.[23]

Adults (Aged 16 Years to 70 Years)

All studies evaluated the antiepileptic efficacy and tolerability of levetiracetam as add-on therapy in adult patients with refractory partial seizures.

Study N051 (Shorvon et al.)[18]: Efficacy data were collected by means of self-reported seizure diaries in which patients or their caregivers noted the date, duration, and description of each seizure. At each study visit, the investigator recorded the number of seizures and classified each according to the ILAE criteria. The total number of seizures that occurred since the previous visit was reported as the seizure count for each seizure type. The primary efficacy variable was the mean number of partial seizures per week defined as the mean number of partial seizures per week over the evaluation period computed during the evaluation period (i.e., seizure frequency). Secondary efficacy variables included the seizure frequency by seizure type and subtype, the responder rate (proportion of patients experiencing a 50% or greater reduction in partial seizure frequency during the evaluation period compared with baseline), and the incidence of seizure-free patients.

Study N132 (Cereghino et al.)[19]: Patients were instructed to maintain a daily record card that included the date, number, duration, and description of seizures throughout each period. Seizure frequency was recorded from the daily record card at each study visit. The primary efficacy variable was the mean number of partial seizures per week (defined as the mean number of partial seizures per week over the evaluation period) computed over the entire 14-week evaluation period. Secondary efficacy variables were median percent reduction compared to baseline, responder rate (number of patients with a minimum of 50% reduction from baseline in partial seizure frequency), and number of seizure-free patients. Response to treatment was recorded according to the following classes of improvement in partial seizure frequency from baseline: up to 25% increase, 25% increase to 24.9% decrease, 25% to 49.9% decrease, 50% to 74.9% decrease, 75% to 99.9% decrease, 100% decrease or seizure free.

At the end of the baseline period and end of treatment the QOLIE-31 was collected.

Study N138 (Ben-Menachem et al.)[20]: Study N138 consisted of an add-on phase followed by a monotherapy phase in which patients were withdrawn from their concomitant AED. The primary efficacy end point for Study N138 pertained to the monotherapy phase of the study, which is not officially part of the Canadian label. **Another efficacy end point** was the seizure frequency, reported as the number of partial seizures per week defined as the mean number of partial seizures per week over the evaluation period, and the responder rate (i.e., the proportion of patients with a reduction in partial seizure frequency of 50% compared with baseline) were presented for the **add-on** phase of the study.

Children (Aged 1 Month to 16 Years)

Aged 1 Month to 4 Years

Study N1009 (Pina-Garza et al.): The primary efficacy variable was the 50% responder rate for partial onset seizures, defined as the percentage of subjects with a 50% or greater reduction in their average daily partial onset seizure frequency, as recorded on the evaluation using 48 hour video EEG compared with the baseline 48 hour video EEG. Secondary efficacy variables included responder rate for all seizures, absolute reduction, and percent reduction in average daily frequency of partial onset and all seizures.

Aged 4 Years to 16 Years

Study N159 (Glauser et al.): The primary efficacy variable was partial seizure frequency (including simple, complex, and secondarily generalized partial seizures) per week during the treatment period. Secondary efficacy variables included responder rates (defined as the percentage of patients experiencing a 50% or greater reduction from baseline in partial seizure frequency during the treatment period), percentage reduction from baseline in partial seizure frequency, percent reduction from baseline in seizure frequency by category (> 25%, 25% to < 50%, 50% to < 75%, 75% to < 100%, and 100%), absolute change from baseline in partial seizure frequency, cumulative percentage of seizure-free patients since the beginning of the evaluation period, and partial seizure frequency per week during the up-titration and evaluation periods.

Children and Adults (Aged 4 Years to 65 Years)

Children and Adults (Aged 12 Years to 65 Years) – Myoclonic Seizures

Study N166 (Noachtar et al.): Patients, or their parents or legal guardians, recorded the date, number, type of seizures, and maximum duration of clusters (counted as 1 seizure) on daily record cards. The primary efficacy variable was the responder rate for myoclonic seizure days per week, defined as a 50% or greater reduction in myoclonic seizure days per week during the treatment period (up-titration and evaluation period) compared with baseline. Myoclonic seizure frequency was not selected as an efficacy variable, as these seizures are frequently difficult to quantify owing to their repetitiveness. Secondary efficacy variables included: responder rates for seizure days per week for all seizure types; median percent reduction from baseline in myoclonic seizure days per week and in all seizure days per week (treatment period); and rates of seizure freedom from myoclonic and all seizure types (treatment and evaluation periods). At the end of the evaluation period, patients and investigators completed a global evaluation scale. Patients aged 16 years or older also completed the patient QOLIE-31-P at the end of the baseline and evaluation periods.

Children and Adult Patients (Aged 4 Years to 65 Years) – Generalized Tonic-Clonic Seizures

Study N1057 (Berkovic et al.): Seizures were recorded in daily diaries by patients or caregivers and reviewed at clinic visits by the investigator. generalized tonic-clonic seizure end points were based on seizure frequency per week, and the reduction from baseline in tonic-clonic seizures was based on the combined (historical and prospective) baseline period. The primary efficacy end point was the percentage reduction from the combined baseline period in generalized tonic-clonic seizure frequency per week over the 24-week treatment period (4 week up-titration plus 20 week evaluation periods). Secondary end points included percentage reduction in seizure days per week (all seizures) from the prospective baseline period; responder rates in terms of generalized tonic-clonic seizure frequency per week and seizure days per week (all seizures) with responses defined as a 50% or greater reduction in the applicable measure from the baseline period to the treatment period (up-titration plus evaluation); and percentage of seizure-free patients (all seizures, including generalized tonic-clonic seizures) during the evaluation and treatment periods (only patients who were free of seizures and completed the evaluation period were considered to be seizure free; patients who discontinued prematurely while being seizure free were considered to be non-seizure free).

The QOLIE-31-P at the end of the baseline and the evaluation periods (or at early discontinuation) was an exploratory variable.

Statistical Analysis

Intention-to-treat (ITT) analyses were performed in all studies. The analysis included all randomized patients who received at least 1 dose of the study drug in studies N051, N132, and N138. In Study N132 the main analysis was based on patients completing the titration period (in addition to responder analysis in all randomized patients). [28]

Adults (Aged 16 Years to 70 Years)

Study N051 (Shorvon et al.)

All statistical analyses were performed using 2-tailed significance tests with the level of significance set at 0.05, unless otherwise specified. To ensure that the overall type I error rate would equal 5%, the level of significance was set at 0.02 for each of the 3 planned pairwise comparisons (levetiracetam 1,000 mg/day or 2,000 mg/day versus placebo and levetiracetam 1,000 mg/day versus 2,000 mg/day) in accordance with the Bonferroni adjustment for multiple comparisons. Continuous variables were analyzed using analysis of covariance (ANCOVA) methodology with the baseline measurement as the covariable. Data were logarithmically transformed and the normality of the residuals was verified using the Shapiro-Wilks statistic, histograms, box plots, and normal probability plots. Pairwise comparisons between the treatment means adjusted on the means of the baseline covariable under analysis of covariance were realized using the Student t-test and 98% CIs. Back transformation of the adjusted means (LSMs) differences with placebo was used to estimate the percentage reduction over placebo. Dichotomous and categorical variables were analyzed

Primary outcome: The primary efficacy variable assessed was the weekly partial seizure frequency. Because seizure frequency did not follow a normal distribution, logarithmic transformation (y = ln[x + 1], where x = weekly seizure frequency) was applied. Treatment

comparisons then were performed on transformed partial seizure frequency in the inferential ITT population during the evaluation period using ANCOVA methodology. Seizure frequency also was calculated for each seizure subtype (simple partial, complex partial, and secondarily generalized). Within each seizure type or subtype, the 3 treatment groups were compared using the Kruskal-Wallis test.

Secondary outcome: The relative reduction in weekly partial seizure frequency was calculated between the baseline and evaluation periods. The variable was analyzed as a continuous variable using the Kruskal-Wallis test and as a binary outcome (responder at 50% and responder at 75%) using a logistic regression model. Contrasts were estimated using the ORs and 98% CIs. The number of patients needed to treat estimation with its 95% to 98% CI was applied on the main binary efficacy outcome (responder rate at 50%).

If values or data were unavailable or missing for a particular study visit, no substitutions were made.

Analysis population: The ITT population consisted of all randomized patients who had received at least 1 dose of study medication, whereas the inferential ITT population included all patients in the ITT population for whom efficacy data were obtained during the evaluation period. Evaluations of efficacy were conducted on the inferential ITT population, and evaluation of safety was conducted on the ITT population.

Study N132 (Cereghino et al.)

All analyses were based on patients who completed titration and entered the evaluation period (placebo group, n = 93; levetiracetam 1,000 mg/day group, n = 94; levetiracetam 3,000 mg/day group, n = 98). At the request of the FDA, analyses of the primary outcome parameter, median percentage reduction in seizure frequency, and the 50% responder rate were also performed on the total randomized population. All analyses were performed with the observed data.

For all efficacy analyses, the Hochberg enhancement to the Bonferroni procedure was used to adjust for multiple comparisons.

Primary outcome: The primary efficacy variable was analyzed using ANCOVA with baseline seizure frequency as the covariate. Additionally, a repeated measures ANCOVA was applied using assessments from each visit during the treatment period.

Secondary outcomes: For secondary efficacy variables based on reduction in seizure frequency during the treatment period compared with baseline, the responder rate was analyzed using a logistic regression model.

Sample size calculation: Results from Phase II studies were evaluated and showed a minimum improvement in seizure reduction of 24% compared to baseline. Therefore, this study was designed to show a difference in log-transformed partial seizure frequency between treatment groups of at least 0.27 (equivalent to a 24% reduction in untransformed seizure frequency as compared to placebo). Projecting a dropout rate of 20%, approximately 300 randomized patients were assumed to be required to achieve 240 fully evaluable patients (80 per treatment group) to be able to detect this difference with 80% power and a type I error of 5%.

Study N138 (Ben-Menachem et al.)

Primary outcome: For the add-on phase, median percentage reduction was analyzed by means of a nonparametric analysis (Kruskal-Wallis). Analyses of the responder rate and the number of seizure-free patients were made using logistic regression and the Fisher's exact test, respectively.

Sample size calculation: This calculation was based on the assumptions of a type I error of 5% and a type II error of 20%. With a 2:1 levetiracetam:placebo randomization ratio, a minimum of 258 evaluable patients were required to detect a 10% difference in the percentage of patients completing monotherapy. Assuming a dropout rate of 30%, approximately 350 patients were required to enter the study.

Analysis population: Efficacy and safety analyses were conducted on the ITT population, which included all patients who were randomized and took at least 1 dose of study medication.

Children (Aged 1 Month to 16 Years)

Study N1009 (Pina-Garza et al.)

Primary outcome: The primary efficacy variable of responder rates was compared using Fisher's exact test with a 0.05, 2-sided significance level. The Cochran-Mantel-Haenszel test was used for comparing responder rates between treatment groups stratified by age group. The youngest 2 age groups (aged 1 month to < 6 months and 6 months to < 1 year) were combined into 1 group for analysis purposes, resulting in 3 age group strata. The absolute and percent reduction in average daily frequency of seizures were compared between treatment groups using the Mann-Whitney U test, and the CI of the median of difference between treatment groups was computed by the Hodges-Lehmann method. The OR with 95% CI was also computed. Descriptive statistics were used for all safety variables.

Sample size: The sample size was calculated based on the primary efficacy variable of responder rate to detect a 26.5% difference between the responder rates in the 2 treatment groups, assuming that 40% of the levetiracetam-treated subjects and 13.5% of the placebo-treated subjects respond to study treatment.

Analysis population: The ITT population consisted of all randomized subjects who took at least 1 dose of study medication. The modified ITT (mITT) population included all ITT subjects who had at least 24 hours of usable baseline video EEG and at least 24 hours of evaluation via video EEG, and also included any randomized subjects who withdrew before the first 24 hours of evaluation via video EEG, with reasons linked to lack or loss of efficacy (nonresponders for the primary efficacy end point). The efficacy analyses were performed on the mITT population, whereas all safety summaries were conducted on the ITT population.

Study N159 (Glauser et al.)

Primary outcome: The primary efficacy variable was analyzed using ANCOVA. The partial seizure frequency per week during the treatment period (up-titration and evaluation periods) was computed. Because the data for seizure frequency per week were not normally distributed, the ANCOVA model was applied on the $\log_e (x + 1)$ transformed data (seizure frequency per week), including treatment as a factor and the $\log_e$ transformed baseline seizure frequency as a covariate. The difference in treatment LSM with a 2-sided 95% CI was computed and expressed as a percentage reduction over placebo: 100 × (1 – exp [LSM

levetiracetam – LSM placebo]). For absolute change and percent of partial seizure frequency per week from baseline, the Kruskal-Wallis test was used for between-treatment comparisons. A logistic regression model was used to compare treatment groups with respect to responder rates over the treatment period. An OR with a 95% CI was also computed.

Sample size: A sample size of 120 patients (60 per treatment arm) was initially chosen to provide 80% power to detect a difference in mean log-transformed seizure frequency per week of 0.223, assuming that the common standard deviation (SD) was 0.43 using a 2-group t-test with a 0.050 2-sided significance level. This common SD value was taken from previous adult epilepsy trials. A difference of 0.223 in log-transformed data corresponded to a reduction from placebo of 20% in seizure frequency per week. All statistical analyses were planned before the unblinding of the trial drug code and were performed using the ITT patient population.

Analysis population: The ITT population consisted of all randomized patients who took at least 1 dose of levetiracetam or placebo and for whom at least 1 post-randomization data point was available. Efficacy and tolerability analyses were conducted by treatment group using descriptive methods for all variables. The 2 methods of presenting the data descriptively included: a frequency distribution containing the numbers of observations and the corresponding percentages for dichotomous and categorical variables (whether ordered or not); and the number of available observations, mean, SD, median, first and third quartiles, minimum, and maximum for continuous variables.

Children and Adults (Aged 4 Years to 65 Years)

Children and Adults (Aged 12 Years to 65 Years) - Myoclonic Seizures

Study N166 (Noachar et al.)

Primary outcome: The primary efficacy and safety analyses were conducted on the ITT population. The treatment OR and 95% CI for the responder rate in myoclonic seizure days per week were estimated by logistic regression analysis, using treatment group as a factor and baseline myoclonic seizure days per week as a covariate. In order to evaluate early onset of action, the first 4 weeks of treatment (up-titration) were subdivided into two 2-week intervals. A post hoc analysis was performed on a subpopulation excluding patients treated with carbamazepine or oxcarbazepine, which are known to potentially aggravate myoclonus, and those with possible protocol violations. The treatment OR and 95% CI for the responder rates in seizure days per week for all seizure types were estimated using logistic regression models similar to those for the primary efficacy variable, including treatment group as a factor and baseline value as a covariate. Seizure freedom rates were compared between treatments using Fisher's exact test. The percentage reductions from baseline in seizure days per week for the entire treatment period were evaluated using descriptive statistics, and the Hodges-Lehmann estimator and its 95% CI were calculated for the median difference between treatment groups. The Wilcoxon-Mann-Whitney test was used to test the hypothesis of equal median reductions from baseline between the treatment groups. The categorical response in myoclonic seizure days and all seizure days was compared between treatment groups using the Cochran-Mantel-Haenszel test based on ranks. TEAEs and changes from baseline in QOLIE-31-P scores, together with a global evaluation scale, were summarized using descriptive statistics.

Sample size: On the basis of a 2-group continuity corrected chi-square test, a sample size of 116 patients (58 patients randomly assigned to each treatment group) was considered sufficient to attain a statistical power of 90% for detecting a treatment difference of 30% in the responder rate, assuming responder rates of 50% and 20% in the levetiracetam and placebo groups, respectively, and using a 5% 2-sided significance level.

Analysis population: The ITT population was defined as all randomized subjects who took at least 1 dose of study medication.

Children and Adults (Aged 4 Years to 65 Years) - Generalized Tonic-Clonic Seizures

Study N1057 (Berkovic et al.)

Primary outcomes: An ANCOVA model was used to assess the superiority of levetiracetam over placebo on percentage reduction from combined baseline to treatment period in generalized tonic-clonic seizure frequency per week (dependent variable) with combined baseline period generalized tonic-clonic seizure frequency per week as covariate. The LSM difference between treatments with 2-sided 95% CIs, was determined; the difference in median percentage reduction between the levetiracetam and placebo groups was assessed using the Mann-Whitney U test.

Secondary outcomes: Median percentage reduction in seizure days per week (all seizures) was compared using the Mann-Whitney U test. Logistic regression analysis compared treatment groups for responder rates in generalized tonic-clonic seizure frequency per week and in seizure days per week (all seizures). Percentage of seizure-free patients (all seizures and generalized tonic-clonic seizures) was analyzed with Fisher's exact test. Descriptive statistics were used to summarize changes from baseline in the incidence of AEs and in the QOLIE-31-P score.

Sample size: A sample size of 77 randomized patients in each treatment group was calculated to yield a power of 80% to detect 25% superiority of levetiracetam over placebo for the primary end point, with an alpha of 0.05. This power assumed a common SD of 0.55, and 2-group t-test of size 0.05.

Analysis population: Since the mITT and per-protocol (PP) analyses yielded similar results to the ITT analysis, this review only presents the results of the ITT analysis. Analyses were performed for the ITT population, comprising all randomized patients who took at least 1 dose of study medication or placebo. Analyses were also performed for an mITT population (all patients in the ITT population with no protocol deviation related to the diagnosis of partial onset seizures, or to the epilepsy etiology determination, as per internal blinded medical review prior to unblinding the study).

Sponsor's Summary of the Results

Patient Disposition

Adults (Aged 16 Years to 70 Years)

Study N051 (Shorvon et al.): No additional details on the screening failures or dropouts were given besides the information in Table 11 as described in "Other." This section encompasses ineligibility, protocol violation, lack of efficacy, the decision of UCB.

Study N132 (Cereghino et al.): The most common reasons for not randomizing patients were failure to fulfill selection criteria (33 patients), consent withdrawn (19), AEs not related to study (14), and protocol violation (12). Reasons for discontinuation were evenly distributed among treatment groups, except in the "other" category, where all discontinued patients were in the levetiracetam 1,000 mg/day group (3 failure to return, 1 lack of efficacy). Of the 18 patients who discontinued because of an adverse event, 7 dropped out during the dose titration period (2 patients in the levetiracetam 1,000 mg/day group; 3 patients in the levetiracetam 3,000 mg/day group, and 2 patients in the placebo group). Eleven patients discontinued during the treatment period (4 patients in the levetiracetam 1,000 mg/day group, 4 patients in the levetiracetam 3,000 mg/day group, and 3 patients in the placebo group).

Study N138 (Ben-Menachem et al.): This study had many phases, namely a part where patients switched from placebo to levetiracetam. These discontinuations were not captured in the Table 11. The discontinuations captured in the table were those that happened after the add-on phase was started.

Children (Aged 1 Month to 16 Years)

Study N159 (Glauser et al.): Before breaking the blinding, 18 patients were excluded, including all 16 patients at 1 site who were excluded because of extensive violation of the protocol and consequent unreliability of the data, and 2 patients because they discontinued before taking any study medication.

Study N1009 (Pina-Garza et al.): Major protocol violations were reported in 17 patients (8 [13.3%] in the levetiracetam group and 9 [16.1%] in the placebo group) and consisted mainly of addition or discontinuation of an AED less than 2 weeks before randomization and no partial onset seizures detected during the 48-hour baseline video EEG.

Children and Adults (Aged 4 Years to 65 Years)

Children and Adults (Aged 12 Years to 65 Years) – Myoclonic Seizures

Study N166 (Noachtar et al.): Overall, 55 of 61 patients (90.2%) in the levetiracetam group and 52 of 60 (86.7%) in the placebo group completed the evaluation period. The majority of subjects (52 receiving levetiracetam; 47 receiving placebo) entered a long-term follow-up study (NCT00150774-N167). The most frequent protocol deviations were related to out-of-range baseline seizure score, prohibited medication or treatment, specific test or examination not done at baseline or showing inappropriate results, and low compliance with study drug intake.

Children and Adult Patients (Aged 4 Years to 65 Years) – Generalized Tonic-Clonic Seizures

Study N1057 (Berkovic et al.): The ITT population comprised all randomized patients since all received at least 1 dose of study medication. However, 1 patient in the levetiracetam group was lost to follow-up immediately after randomization (with no efficacy or safety assessments) and another patient provided only seizure occurrence (not frequency) data. Thus, 78 levetiracetam-treated patients were evaluable for efficacy and 79 for safety.

Table 11: Patient Disposition – Partial Seizures in Adults

Patient disposition		Study N051 Shorvon et al. (2000)			Study N132 Cereghino et al. 2000			Study N138 Ben-Menachem et al. (2000)	
		LEV 1,000 mg/day	LEV 2,000 mg/day	Placebo	LEV 1,000 mg/day	LEV 3,000 mg/day	Placebo	LEV 3,000 mg/day	Placebo
Screened, N		392			385			343	
Randomized, N		106	106	112	98	101	95	181	105
Discontinued, n (%)		11%	18%	13%	12 (12.2%)	8 (7.9%)	6 (6.3%)	22 (12.2%)[a]	12 (11.4%)[a]
Reason for discontinuation n (%)	Adverse events	8 (7.5%)	15 (14.2%)	6 (5.4%)	6	7	5	8[a]	7[a]
	Lost to follow-up	NA	NA	NA	3	0	0	0	NA
	Withdrew consent	2 (1.9%)	3 (2.8%)	5 (4.5%)	2	1	1	5[a]	1[a]
	Protocol violation	NA	NA	NA	NA	NA	NA	6[a]	3[a]
	Lack or loss efficiency	NA	NA	NA	NA	NA	NA	3[a]	1[a]
	Other	2 (1.9%)	1 (0.9%)	4 (3.6%)	1	0	0	0	NA
ITT, n		106	106	112	98	101	95	181	105
PP, n		NA	NA	NA	NA	NA	NA	NA	NA
Safety, n		106	106	112	98	101	95	181	105

ITT = intention to treat; LEV : levetiracetam; NA = not mentioned or not available; PP = per protocol.

[a] The incidence of adverse events compared with placebo is reported only for the add-on phase.

Source: Ben-Menachem et al. (2000),[20] Cereghino et al. (2000),[19] Shorvon et al. (2000).[18]

Table 12: Patient Disposition - Partial Seizures in Children (Aged 1 Month to 16 Years) and Generalized Seizures in Children and Adults (Aged 4 Years to 65 Years)

Patient disposition		Study N159 Glauser et al. (2006)		Study N1009 Pina-Garza et al. (2009)		Study N166 Noachtar et al. (2008)		Study N1057 Berkovic et al. (2007)	
		LEV	Placebo	LEV oral solution	Placebo	LEV	Placebo	LEV	Placebo
Screened, N		282		175		144		229	
Randomized, N		216		60	56	62	60	80	84
Discontinued, n (%)		7 (7)	14 (14)	2 (3)	3 (5)	7 (11.2)	8 (13)	10 (12.5)	14 (16.7)
Reason for discontinuation n (%)	Adverse events	5 (5%)	9 (9.3%)	2	1	3	1	1	4
	Lost to follow-up	1	2	0	NA	2	1	5	NA
	Withdrew consent	NA	NA	0	1	2	1	4	1
	Protocol violation	NA	NA	0	1	NA	1	NA	1
	Lack or loss efficiency	0	2	NA	NA	NA	4	NA	3
	Other	1	1			NA	NA		5
ITT, n		101	97	60	56	61	60	80	84
PP, n		NA	NA	NA	NA	NA	NA	NA	NA
Safety, n		101	97	60	53	61	60	79	84

ITT = intention to treat; LEV = levetiracetam; NA = not mentioned or not available; PP = per protocol.

Source: Berkovic et al. (2007),[24] Glauser et al. (2006),[21] Noachtar et al. (2008),[23] Pina-Garza et al. (2009).[22]

Exposure to Study Treatments

Study Treatments

All patients were on a stable concomitant medication and on levetiracetam or placebo. The maximal dose of 3,000 mg/day was a treatment arm in Study N132 (Cereghino et al.) and in Study N132 (Ben-Menachem et al.). In the pediatric trials the dosage was administered by weight with maximal target dosages. Patients who could not tolerate maximal dosages could typically fall back to 40 mg/kg or 2,000 mg/day.

Concomitant Medications

Patients were allowed to be on 1 or more concomitant medications as levetiracetam was studied as an add-on therapy. Most patients were on 2 concomitant medications.

Among the publications listed in the product monograph and described in this document, allowed concomitant medications in participating patients generally included: carbamazepine, lamotrigine, valproic acid, topiramate, phenobarbital, oxcarbazemine, clobazam, clonazepam, vigabatrin, phenytoin, gabapentin, diazepam, ethosuximide, primidone, and valproate.

Efficacy

Note: CADTH prefers CI values on top of the P values; however, given that Pendopharm was not the sponsor of the studies but UCB Pharma was, we do not have the Clinical Study Reports that might contain this level of detail.

Comparison of Efficacy Results of all Studies

Controlled Clinical Trials Conducted With Levetiracetam Oral Tablets and Solution

Levetiracetam As Adjunctive Therapy in the Treatment of Partial Onset Seizures in Adults (Aged 16 Years to 70 Years)

The 3 adequate and well-controlled clinical trials (studies N051, N132, and N138), taken together, provide substantial evidence of the effectiveness of levetiracetam as adjunctive treatment for partial onset seizures in adults with epilepsy. Levetiracetam as add-on medication in daily doses of 1,000 to 3,000 mg significantly reduces seizure frequency in patients with refractory partial epilepsy when compared to placebo. Higher doses did not increase efficacy but increased the rate of side effects. Although the clinical data are judged to be adequate to permit the use of levetiracetam as add-on treatment in partial seizures, data were considered insufficient by the Committee for Medicinal Products for Human Use (CHMP) to justify the use of levetiracetam as monotherapy. Based on the review of the benefit and risk profile of Keppra, the CHMP considered it be used as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalization in patients with epilepsy.

Levetiracetam as Adjunctive Therapy in the Treatment of Partial Onset Seizures in Children Aged 4 Years to 16 Years

Study N159 (Glauser et al.): Levetiracetam was effective in treating pediatric patients with refractory partial onset seizures. Levetiracetam provided clinically relevant, statistically significant reductions over placebo in partial onset seizure frequency per week among children aged 4 years to 16 years during the treatment period. Levetiracetam also provided clinically relevant, statistically significant reductions over placebo in total seizure frequency

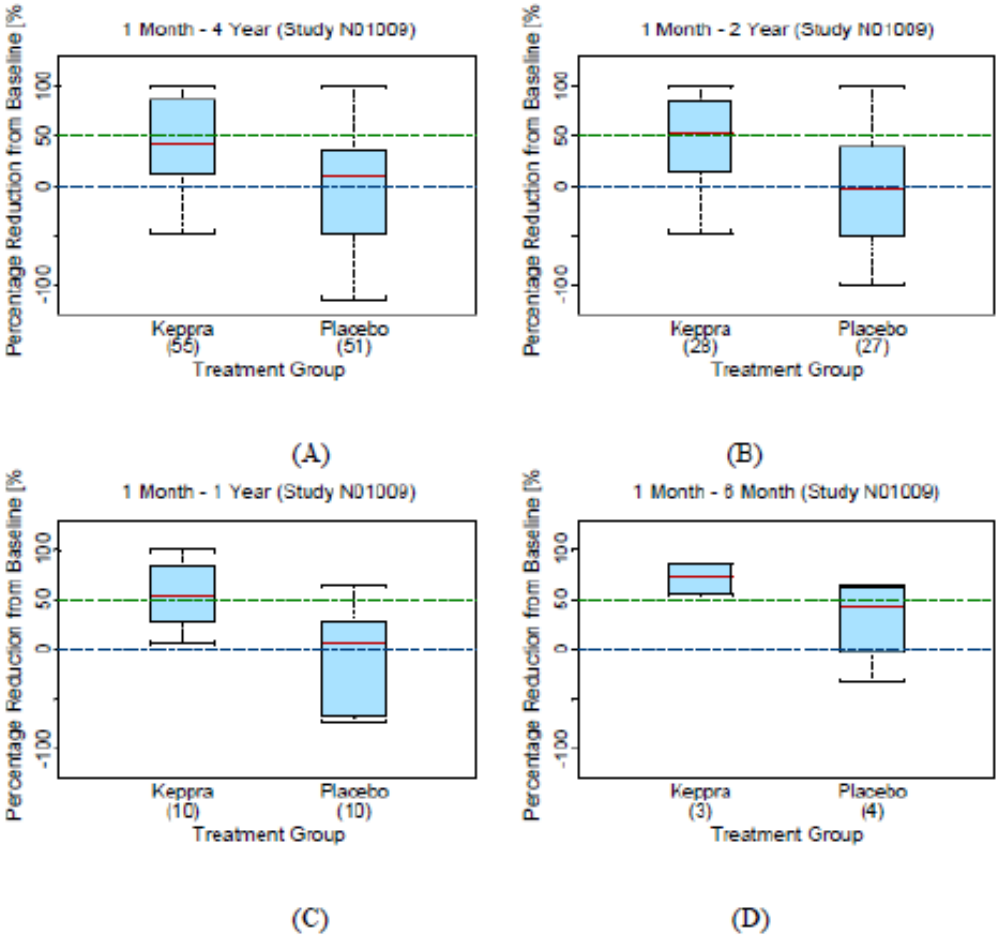
per week over the treatment period. The percentage of patients with a 50% or greater reduction from baseline in seizure frequency per week over the treatment period was significantly larger for levetiracetam than for placebo for partial onset seizures and total seizures. The change from baseline in partial onset seizure frequency per week over the treatment period was significantly larger for levetiracetam than for placebo for both the absolute change and median percent change from baseline. The percent of patients who were continuously seizure free during the evaluation period was 10.2% (7 patients) for levetiracetam as compared to 3.2% (1 patient) for placebo. Reductions from baseline in median seizure frequency per week were observed across subgroups based on age, gender, and study drug dose. Significant efficacy was seen at each dose level, during up-titration beginning with dose levels of 20 mg/kg per day.

Levetiracetam as Adjunctive Therapy in the Treatment of Partial Onset Seizures in Infants and Children Aged 1 Month to Less Than 4 Years

Study N1009 (Pina-Garza et al.): Levetiracetam is efficacious in the treatment of pediatric patients as young as 1 month to 6 months by consistently exhibiting greater percent seizure reduction from baseline compared to placebo group across different age groups. Even though the significant levetiracetam treatment effect has been demonstrated for all pediatric patients aged 1 month to 4 years, because of the small sample size, it is not feasible to demonstrate statistically significant treatment effect within each age subgroup. Therefore, the FDA reviewers explored additional evidence by comparing the distribution of percentage change from baseline in the levetiracetam-treated group with the placebo group, in order to understand whether there was a consistent effectiveness following levetiracetam treatment among pediatric patients within different age subgroups. If the significant treatment effect was only derived by patients aged 2 years or older, similar response was expected between levetiracetam and placebo after older patients (i.e., aged 2 years or older) were removed from the analysis dataset. The analysis indicated consistent effectiveness in pediatric patients even 1 month to 6 months of age (Figure 8).

For all patients aged 1 month to 4 years tested in Study N1009 (N = 106), the placebo did not seem to provide additional benefit, because the median percentage change from baseline was approximately 0. However, the median percentage change from baseline was about 50% for the levetiracetam group, which was much higher than the observation from the placebo group. A similar pattern could be found in pediatric patients less than 2 years old and less than 1 year old. Even though there were only 7 pediatric patients aged 1 month to 6 months in the study, the levetiracetam treatment group still demonstrated a larger percentage change from baseline as compared to placebo. In summary, the levetiracetam treatment effect appeared to be consistent across all age groups, even for patients aged 1 month to 6 months.

Figure 8: Demonstration of Consistent Levetiracetam Treatment Effect in Different Age Groups



Source: Common technical document. 2.7.3 Summary of Clinical Efficacy.[28]

Levetiracetam as Adjunctive Therapy in the Treatment of Myoclonic Seizures in Patients (Children and Adults, Aged 12 Years to 65 Years) With JME

Study N166 (Noachtar et al.): The clinical efficacy program was based on 1 placebo-controlled study (N166) and its open-label extension study (N167, not described here). The benefit of levetiracetam in this indication was supported by the primary end point with a 50% or greater responder rate in myoclonic seizure days per week of 58.3% for the subjects in the levetiracetam group compared to 23.3% for the subjects in the placebo group. The OR (levetiracetam versus placebo) was 4.77 times higher with levetiracetam than on placebo. This difference was statistically significant (P = 0.0002). These results were confirmed by the sensitivity analysis on the PP population. The CHMP Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Epilepsy recommends that the analysis of efficacy should be based on the period when patients are established on a fixed dose of the study drug. In Study N166, the comparison was between the baseline and the treatment period (including both up-titration and evaluation periods). This primary end point

was defined in the original protocol, the finalization of which preceded the current CHMP guideline. However, Keppra's sponsor provided a supplementary analysis for the primary efficacy parameter based on the evaluation period only, which showed similar responder rates as in the primary analysis. The efficacy of Keppra in the treatment of myoclonic seizures was also supported by secondary end points, including those analyses performed on seizure days per week and on seizure frequency per week for myoclonic seizures and for all seizures aggregated.

A therapeutic benefit of levetiracetam in the reduction of myoclonic seizure frequency was already observed during the first 2 weeks of treatment at a daily dose of 1,000 mg. Thirteen (21.7%) subjects in the levetiracetam group were seizure free during the evaluation period compared to 2 (3.4%) subjects in the placebo group. Eight (13.3%) of these subjects in the study drug group were seizure free for the entire treatment period (up-titration plus evaluation) compared to 1 (1.7%) subject in the placebo group. Most subjects on levetiracetam with a high number of myoclonic seizure days during baseline substantially improved during treatment. Although Study N166 was not designed as a dose-response study, these elements suggest that levetiracetam was efficient in reducing myoclonic seizures already at the doses of 1,000 and 2,000 mg/day.

Levetiracetam as Adjunctive Therapy in the Treatment of PGTC Seizures in Patients (Children and Adults With Idiopathic Generalized Epilepsy, Aged 4 Years to 65 Years)

Study N1057 (Berkovic et al.): The mean percent reduction in PGTC seizure frequency from the baseline to the treatment period (primary end point) was statistically significant in the levetiracetam group (56.5% in the levetiracetam group versus 28.2% for placebo group). The responder rate was also significantly higher in the levetiracetam group (68.4% versus 44.0%). In addition, PGTC seizure freedom was achieved in 24.1% in the levetiracetam group compared to 7.1% in the placebo group for the group of completers over the treatment period. The CHMP Epilepsy Guidelines state that the analysis of efficacy should be based on the period when patients are stabilized on a fixed dose of the study drug (i.e., the evaluation period in this case) and not the treatment period (which includes up-titration plus evaluation phases). However, the analyses performed showed similar results for both periods. Therefore, the efficacy of levetiracetam as adjunctive therapy for PGTC seizures was considered to be sufficiently demonstrated.

Efficacy Outcome 1: Number of Weekly Seizures

Table 13: Median Reduction in Number of Weekly Seizures (%, ITT analysis)

Study and drug	N	Baseline	End of treatment		Treatment group difference vs. control		
		Median (SD)	Median (SD)	Median change from baseline (SE)	N	Median (or mean) difference (95% CI)	P value
N051 (Shorvon et al.) – 12 weeks evaluation time							
LEV 1,000 mg/day	106	2.82	—	17.7%[a]	—	Mean difference[b] = 16.4% (98% CI, 2.7 to 28.1)	0.006
LEV 2,000 mg/day	106	2.58	—	26.5%[a]	—	Mean difference[b] = 17.7% (98% CI, 4.1 to 29.4)	0.003
Placebo	112	2.50	—	6.1%[a]	—	—	—

Study and drug	N	Baseline	End of treatment		Treatment group difference vs. control		
		Median (SD)	Median (SD)	Median change from baseline (SE)	N	Median (or mean) difference (95% CI)	P value
N132 (Cereghino et al.) – at 18 weeks evaluation period plus titration							
LEV 1,000 mg/day	98	2.53	—	36.9%	—	Median difference = 26.1%	< 0.001
LEV 3,000 mg/day	101	2.08	—	38.1%	—	Median difference = 30.1%	< 0.001
Placebo	95	1.77	—	6.9 %	—	—	< 0.001
N138 (Ben-Menachem et al.) – from baseline to add-on phase							
LEV 3000/mg day	181	1.69	—	39.9%	—	Median difference = 22.9% (98% CI, 14.3 to 29.4)	< 0.001
Placebo	105	1.75	—	7.2%	—	—	< 0.001
N159 (Glauser et al.) – evaluation period 14 weeks							
LEV 60 mg/kg/d	101	4.7	—	43.8%	—	Median difference = 26.8% (14 to 37.6)	0.0002
Placebo	97	5.3	—	23.3%	—	—	—
N1057 (Berkovic et al.) – 24 weeks evaluation period plus titration							
LEV[c]	78	0.62 (mean = 1.70)	—	77.8% (mean = 56.49)[d] (77.6%)[e]	—	LSM difference = 28.31 (8.97 to 47.64)[d]	0.0004[d]
Placebo	84	0.62 (mean = 1.20)	—	47.7% (mean = 28.19)[d] (44.6%)[e]	—	—	—

CI = confidence interval; ITT = intention to treat; LEV = levetiracetam; LSM = least squares mean; SD = standard deviation; SE = standard error; vs. = versus.

[a] All partial subtypes (simple and complex).

[b] Mean difference: Reduction over placebo: back transformation of the difference of log seizure frequency between LEV 1,000 mg/day or 2,000 mg/day and placebo, expressed in% of placebo = 100 [I - exp (LSM LEV- LSM placebo)].

[c] LEV dosing for adults was 3,000 mg/day and for children was 60 mg/kg per day during the 4-week up-titration phase of the 20-week evaluation phase.

[d] Data from Health Canada reviewer report[13], added by CADTH.

[e] During the 20-week evaluation period LEV dosing in adults was 3,000 mg/day and in children was 60 mg/kg per day; the median reduction of the seizure frequency in the LEV group was 77.8% vs. 47.7% in the placebo group (P < 0.001). In the 24-week treatment period (titration plus evaluation period) LEV dosing was 1,000 to 3,000 mg/day in adults and 20 mg/kg to 60 mg/kg per day in children; the median reduction of the seizure frequency in the LEV group was 77.6% vs. 44.6% in the placebo group (P < 0.001).

Source: Ben-Menachem (2.7.3 Summary Clinical, p. 14),[28] Berkovic et al.,[24] Cereghino et al.,[19] Glauser et al.,[21] Health Canada reviewer report,[13] Shorvon et al.[18]

Efficacy Outcome 2: A 50% or Greater Responder Rate

Table 14: Proportion of Patients With 50% or Greater Reduction of Seizure Frequency (Responder, %, ITT analysis)

Study and drug	N	End of treatment	Treatment group difference vs. control	
		Proportion of patients with ≥ 50% reduction	OR (95% CI)	P value
N051 (Shorvon et al.) – 12 weeks evaluation period				
LEV 1,000 mg/day	101	22.8%	NR[a]	P < 0.02
LEV 2,000 mg/day	95	31.6%	NR[a]	P < 0.001
Placebo	106	10.4%	NR	NR
N132 (Cereghino et al.) – at 18 weeks evaluation period plus titration				
LEV 1,000 mg/day	98	37.1%	NR	< 0.001

Study and drug	N	End of treatment	Treatment group difference vs. control	
		Proportion of patients with ≥ 50% reduction	OR (95% CI)	P value
LEV 3,000 mg/day	101	39.6%	NR	< 0.001
Placebo	95	7.4%	NR	< 0.001
N138 (Ben-Menachem et al.) – add-on phase				
LEV 3000/mg day	181	42.1%	NR	< 0.001
Placebo	105	16.7%	NR	< 0.001
N159 (Glauser et al.) – evaluation period 14 weeks				
LEV 60 mg/kg/d	101	44.6%	3.3 (1.75 to 6.24)	0.0002
Placebo	97	19.6%	NR	NR
N1009 (Pina-Garza et al.) – evaluation period 5 days				
LEV oral solution[b]	58 (mITT)	43.1%	3.11(1.22 to 8.26) mITT[c]	0.013
Placebo	51 (mITT)	19.6%	NR	NR
N166 (Noachtar et al.) – 16-week evaluation period				
LEV 3,000 mg/day	60	58.3%	4.77 (2.12 to 10.77))	< 0.001
Placebo	60	23.3%	NR	NR
N1057 (Berkovic et al.) – 24 weeks evaluation period plus titration				
LEV[d]	79	20 week evaluation: 68.4% 24 week evaluatioin: (77.2%)[e]	3.28 (1.68 to 6.38)[e]	0.004
Placebo	74	20 week evaluation: 44.0% 24 week evaluation: (45.2%)[e]	NR	NR

CI = confidence interval; ITT = intention to treat; LEV = levetiracetam; OR = odds ratio; vs. = versus.

[a] The number of patients needed to treat to get a responder with a 50% or greater reduction in seizure frequency during treatment with LEV was 6.9 (95% CI, 4.3 to 17.9) for the 1,000 mg group and 3.5 (95% CI, 2.6 to 5.4) for the 2,000 mg group. In addition, 3.7% of patients in the placebo group experienced a 75% or greater reduction in seizure frequency, compared with 10.9% (P = 0.03) for the 1,000 mg group and 16.8% (P = 0.001) for the 2,000 mg group. Five patients (5%) in the 1,000 mg group and 2 patients (2%) in the 2,000 mg group were seizure free during the evaluation period, compared with 1 patient (0.9%) in the placebo group who reported no seizures until study withdrawal at day 29.

[b] The oral solution used was 10% LEV (100 mg/mL). Dosing for patients aged 1 month to less than 6 months was LEV at 20 mg/kg per day on day 1 with maintenance dosing of 40 mg/kg per day; for patients aged 6 months to less than 4 years, LEV dosing started at 25 mg/kg per day on day 1 and maintenance dosing was 50 mg/kg per day.

[c] The results were consistent across all age groups (Figure 3), although a slightly higher responder rate and OR were observed in the subgroup of infants aged 1 month to less than 12 months than in other subgroups (OR = 4.8; 95% CI, 0.5 to 62.3, compared with OR = 2.7; 95% CI, 0.5 to 15.4 for the 12 month to less than 24 month age group and OR = 2.9, 95% CI, 0.7 to 14.7 for the 24 month to less than 48 month age group).

[d] In adults dosing was LEV 3,000 mg/day and in children LEV dosing was 60 mg/kg per day during the 20-week evaluation phase.

[e] During the 20-week evaluation period, LEV dosing was 3,000 mg/day in adults and 60 mg/kg per day in children. The percentage of responders in the LEV group was 68.4 % vs. 44.0 % in the placebo group (P < 0.001). In the 24-week treatment period (titration plus evaluation period), LEV dosing was 1,000 mg/day to 3,000 mg/day in adults and 20 mg to 60 mg/kg per day in children. The percentage of responders in the LEV group was 72.2% vs. 45.2% in the placebo group (P < 0.001). The OR (95% CI) for the 24-week treatment period (titration plus evaluation period) was 3.28 (1.68 to 6.38).[24]

Source: Ben-Menachem et al.,[20] Berkovic et al.,[24] Cereghino et al.,[19] Glauser et al.,[21] Noachtar et al.,[23] Pina-Garza et al.,[22] Shorvon et al.[18]

Harms

Safety Evaluation Plan[27]

Overall Safety Evaluation Plan and Narratives of Safety Studies

The AED levetiracetam was approved in November 1999 as add-on therapy for the treatment of partial onset seizures in adults based on its safety profile as well as its effectiveness. Since then, the innovator has conducted safety and efficacy studies in JME

and PGTC in adults and pediatric patients. The safety evidence has been well documented in literature and levetiracetam continues to gain considerable market experience. In Canada, levetiracetam is given as an off-label extemporaneous suspension as the current label has no pediatric indication, and neither an oral solution nor IV formulation is approved. Such lack of a suitable pediatric formulation leaves children at risk of increased AEs, suboptimal dosing with consequent risk of therapeutic failure, and noncompliance due to poor palatability.[28] Levetiracetam is available in other jurisdictions (EU and US) in dosage formats amenable to patients who cannot swallow and young children.[29]

This Summary of Clinical Safety includes a review of the most significant safety data derived from the pivotal trials conducted with Keppra from publicly available data as well as safety data collected from various sources such as foreign health authority reviews from US and Europe. Actual use data for levetiracetam has also been summarized. The clinical development program for pdp-levETIRAcetam oral solution and pdp-levETIRAcetam IV injection was discussed with Health Canada on April 11, 2017 and was found acceptable for filing as a New Drug Submission based on evidence available in published literature, as per the Health Canada Guidance Document: Drug Submissions Relying on Third-Party Data (Literature and Market Experience). Accordingly, a summary of clinical studies that supported the approvals of Keppra for the proposed indications is presented as well as a Cochrane systematic review of literature. A list of foreign reviews referenced in this safety overview can be found in in Module 1.2.7 International Registration Status.

Overview of Safety

Source: Product Monograph of pdp-levETIRAcetam[9]

In well-controlled clinical studies, the most frequently reported AEs associated with the use of levetiracetam in combination with other AEDs, not seen at an equivalent frequency among placebo-treated patients, were somnolence, asthenia, dizziness, infection, and most notably in pediatrics, altered mood and behaviour, as well as decreased appetite. Of the most frequently reported AEs, asthenia, somnolence, and dizziness appeared to occur predominantly during the first 4 weeks of treatment with levetiracetam.

The adverse reaction profile of levetiracetam is generally similar across age groups and across the approved epilepsy indications. Safety results in pediatric patients in placebo-controlled clinical studies were consistent with the safety profile of levetiracetam in adults except for behavioural and psychological adverse reactions, as well as anorexia or decreased appetite, which were more common in children than in adults.

Suicide ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. All patients treated with AEDs, irrespective of indication, should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered.

Table 15: Summary of Harms Data – Adults (Aged 16 Years to 70 Years)

Adverse events	Study N051 (Shorvon et al. 2000)[18]			Study N132 Cereghino et al. (2000)[19]			Study N138 Ben-Menachem et al. (2000)[20]	
	LEV 1,000 mg/day	LEV 2,000 mg/day	Placebo	LEV 1,000 mg/day	LEV 3,000 mg/day	Placebo	LEV 3,000 mg/day	Placebo
Patients with at least 1 adverse event								
n (%)	70.8%	75.5%	73.2%	87 (88.8%)	90 (89.1%)	84 (88.4%)	55%	53%
Most common events	Asthenia, headache, accidental injury, and somnolence			NA	NA	NA	Asthenia, infection, and somnolence	
Patients with at least 1 serious adverse event								
n (%)	2	8	3	7 (7.1%)[a]	2 (2%)[a]	10 (10.5%)[a]	4	1 (confusion)
Most common events	NA	NA	NA	NA	NA	NA	Maculopapular rash, suspected spontaneous abortion, and convulsions	
Withdrawals due to adverse events								
n (%)	8 (7.5%)	15 (14.2%)	6 (5.4%)	6 (6.1%)	7 (6.9%)	5 (5.3%)	13	8
Most common events	NA	NA	NA	Most commonly somnolence			NA	NA
Adverse events of special interest								
Adverse events of special interest, n (%)	NA	NA	NA	NA	NA	NA	NA	NA

NA = not mentioned or not available; LEV: levetiracetam.

[a] There were 2 deaths during the study and both were sudden and unexpected. One patient died during the baseline period before randomization after having a severe seizure; that death was attributed to the seizure disorder. The second patient who died had been randomized to placebo treatment.

Source: Shorvon et al. (2000), Cereghino et al. (2000), Ben-Menachem et al. (2000).

Table 16: Summary of Harms Data – Children and Adults (Aged 1 Month to 65 Years)

Adverse events	Study N159 Glauser et al. (2006)		Study N1009 Pina-Garza et al. (2009)		Study N166 Noachtar et al. (2008)		Study N1057 Berkovic et al. (2007)	
	LEV (N = 101)	Placebo (N = 97)	LEV oral solution (N = 60)	Placebo (N = 56)	LEV (N = 101)	Placebo (N = 97)	LEV (N = 60)	Placebo (N = 56)
Patients with at least 1 adverse event								
n (%)	89 (88.1%)[a]	89 (91.8%)[a]	33 (55%)	25 (44.6%)	75%	66.7%	57 (72.2)	57 (67.9)
Most common adverse events	Somnolence, accidental injury, vomiting, anorexia, rhinitis, hostility, increased cough, pharyngitis, and nervousness		Somnolence and irritability		Hypersomnia, agitation, and depression	Hypersomnia, agitation, and depression	Nasopharyngitis, headache, fatigue, dizziness, and diarrhea	
Patients with at least 1 serious adverse event								
n (%)	8 (7.9%)[b]	9 (9.3%)[b]	2	1	4	1	3 (3.8)	5 (5.9)
Most common events	NA	NA	Food aversion, pyrexia, convulsion, and urinary tract infection		NA	NA	NA	NR
Withdrawals due to adverse events								
n (%)	5 (5%)	9 (9.3%)	2	1	3	1	1 (1.3%)	4 (4.8%)
Most common events	NA	NA	Convulsion and food aversion		Hypersomnia, agitation, depression, anxiety, and insomnia		NA	NA
Adverse events of special interest								
Adverse events of special interest, n (%)	NA	NA	NA	NA	NA	NA	NA	NA

NA = not mentioned or not available; LEV = levetiracetam.

[a] At least 1 treatment-emergent adverse event considered to be related to the study drug was reported in 56 levetiracetam-treated patients (55.4%) and 39 placebo patients (40.2%).

[b] None were considered by the investigator to be possibly related to the study drug, except for 1 case of convulsion in a patient randomized to placebo.

Source: Glauser et al. (2006),[21] Pina-Garza et al. (2009),[22] Noachtar et al. (2008),[23] Berkovic et al. (2007).[24]

Bioequivalence

Oral levetiracetam solution has a long history of use of more than 10 years. Approval of the levetiracetam oral solution in the US and EU was based on requisite bioequivalence and chemistry data. Other than a safety update, no new clinical efficacy data were included. The development plan for approval of the 100 mg/mL levetiracetam oral solution includes a bioequivalence study between Keppra oral solution (10% levetiracetam) and Keppra tablets (750 mg) (Coupez et al.[30]). Moreover, the pharmaceutical equivalence between [redacted] has been demonstrated in an in vitro comparative analysis. This approach was also endorsed by Health Canada.

Figure 9: [Figure Redacted at Request of Sponsor]

[redacted]

This figure was redacted at the request of the sponsor.

Coupez et al. is a phase I single-centre, randomized, open-label, 2-way crossover, single-dose bioequivalence study. Oral levetiracetam solution and oral levetiracetam tablets confirmed that a 10% oral solution of levetiracetam was bioequivalent to the 750 mg oral tablet. The mean levetiracetam plasma concentration time curves and PK parameters were essentially identical for the oral 10% solution and tablet and consistent with previously reported levetiracetam PK. The 90% confidence limits of the geometric mean ratio of the 2 formulations for area under the curve (AUC) from time 0 to infinity (0-∞), AUC from time 0 to the last measurable time point (0-t), and maximum plasma concentration (C_{max}) were within the 80% to 125% range, demonstrating bioequivalence of the 2 formulations.

The in vitro testing was done [redacted] The Health Canada Guidance for Industry - Pharmaceutical Quality of Aqueous Solutions – includes recommendations for testing that can be used [redacted]

Available information on the innovator oral solution [redacted]. Furthermore, the comparison of the relevant [redacted]

Table 17: Bioequivalence Data

Pharmacokinetics	Levetiracetam 10% oral solution N = 24	Levetiracetam tablet N = 24	Comparison
AUC (mcg•hour/mL) mean (SD)	201.7 (33.6)	204.7 (33.6)	The 90% confidence limits for each of these pharmacokinetic variables were within the 80% to 125% range to conclude bioequivalence of the 2 levetiracetam formulations.
$AUC_{(0-t)}$ (mcg•hour/mL) mean (SD)	193.0 (35.3)	195.2 (35.0)	
C_{max} (mcg•hour/mL) mean (SD)	21.1 (4.0)	20.3 (3.9)	
T_{max} (median hour) (range)	0.50 (0.33 to 1.50)	0.75 (0.50 to 2.00)	
Mean resistance time (SD) (hour)	10.3 (1.20)	10.6 (1.46)	
λz (1/hour) mean (SD)	0.0955 (0.0119)	0.0953 (0.0135)	
T1/2 (hour) mean (SD)	7.4 (0.87)	7.4 (1.02)	
CL/F/WT (mL/minute/kg) mean (SD)	0.86 (0.14)	0.85 (0.15)	
Vz/F/WT (L/kg) mean (SD)	0.54 (0.08)	0.54 (0.08)	

AUC = area under the plasma concentration time curve from time 0 to infinity; $AUC_{(0-t)}$ = AUC from time 0 to last measurable time point; CL/F/WT = apparent plasma clearance normalized by body weight; C_{max} = maximum plasma concentration; λz = terminal elimination rate constant; MRT = mean residence time; SD = standard deviation; T1/2 = elimination half-life; T_{max} = time to C_{max}; Vz/F/WT = apparent volume of distribution normalized by body weight.

CADTH's Critical Appraisal of the Clinical Evidence

CADTH conducted a critical appraisal of the clinical studies for levetiracetam oral solution based on the summary of the evidence provided by the sponsor.

Internal Validity

Given that the body of evidence included in the sponsor's summary was based on third-party data, only publications of the included studies were available. Therefore, outcomes and results may be subject to potential reporting bias, which make the thorough accurate critical appraisal more difficult.

Based on information available in the summary of evidence submitted by the sponsor, a number of methodological strengths of study design were demonstrated; all 7 included trials[18-24] were prospective, multi-centre, double-blind, randomized, placebo-controlled trials. Appropriate randomization and allocation concealment procedures were clearly described in the 2 trials in children (N159 and N1009) and in the 2 studies including a mixed population of children and adults (N166 and N1057),[21-24] To reduce bias and achieve balance in the allocation of participants to treatment arms, randomization was conducted using a block size of 4 in Study N159 (in children, aged 4 years to 16 years)[21] and Study N166 (in mixed population of children and adults, aged 12 years to 65 years).[23] Randomization was stratified by geographical region and/or age in Study N1009 (children aged 1 month to < 4 years), [22] Study N166 (in children and adult, aged 12 years to 65 years)[23] and Study N1057 (children and adult, aged 4 years to 65 years).[24] However, the randomization methods and allocation concealment information were not reported in any of the trials conducted in adults (studies N051,[18] N132,[19] and N138[20]). Overall, the design features as described above minimize the risk of performance bias and detection bias.

Baseline demographic and disease characteristics were generally well balanced across treatment arms in each study at baseline. Gender was imbalanced in some of the studies (N132[19] and N166[23]). In Study 132,[19] higher seizure frequency at baseline was observed in the levetiracetam 1,000 mg group. However, the clinical expert CADTH consulted for the

review indicated that these minor imbalances between treatment groups were not expected to have an impact on the response to treatment.

The duration of the double-blind RCT phase (not including titration phase) in all trials except Study N1009 was 12 weeks[18,23] to 24 weeks,[24] which was considered to be the standard duration used in clinical trials for epilepsy and of adequate duration to demonstrate a treatment effect by the clinical expert consulted by CADTH. However, according to the clinical expert consulted by CADTH, considering the irregular and unpredictable occurrence of seizures, a longer duration of therapy would provide stronger evidence of clinically important treatment effects. The double-blind RCT phase duration of Study N1009 [22] was 5 days, which is insufficient to estimate the efficacy and safety of levetiracetam oral solution.

Overall, the proportion of patients who discontinued from the trials was low (< 15%) across the trials (except for Study N051[18], in which 18% patients in levetiracetam 2,000 mg/day group were discontinued from the study,[18] and Study N1057, in which 16.7% patients in the placebo group discontinued from the study,[24]). The imbalance of the discontinuation between treatment groups in studies N051, N132, N159, and N1057 was unlikely to have an impact on the efficacy analysis.

The reduction of the frequency of seizures (the median or mean reduction of seizures frequency per week) was the primary efficacy outcome assessed in 5 trials (studies N051,[18] N132,[19] N138[20], N159[21], and N1057 [24]). The primary efficacy outcome in Study N1009 [22] (in children aged 1 month to < 4 years of age with partial onset seizures) and Study N166 [23] was the proportion of patients who achieved a 50% or greater reduction of the seizure frequency at the end of the trial (i.e., the responder). The clinical expert consulted for the review indicated that both reduction of the frequency of seizures and the proportion of the responder were standard and acceptable clinical outcomes in the clinical trials. A statistically significant reduction in seizure frequency and/or statistically significant greater proportion of responders was demonstrated with levetiracetam treatment in all 7 trials. The clinical expert indicated that the clinical significance of the reduction of seizure frequency depends on the baseline seizure frequency and that a response to treatment would be for the patient to remain seizure free for a minimum of 3 times the interseizure interval or 12 months.

In Study N1009,[22] the seizure frequency was assessed based on a 48-hour EEG over a 5-day inpatient treatment period (1-day up-titration 48-hour evaluation via video EEG in the last 2 days), which is considered a reliable method to identify and characterize partial onset seizures in infants and young children.[13,14] In the remaining 6 trials, the seizure frequency and seizure types were recorded by patients, and/or caregivers or legal guardians by filling in a daily record card which was returned at each study visit.[18-21,23,24] Although this is a standard method of reporting outcomes related to seizure frequency in clinical trials of AEDs, patient- or caregiver-reported outcomes are subject to individual variability in reporting accuracy (e.g., missing or misclassification of seizures) and completion.

ITT analyses were performed in all trials except 2 trials (N1009[22] and N132[19]). In Study N1009, mITT analysis was performed based on the population included all ITT patients who had at least 24 hours of usable baseline video EEG and at least 24 hours of evaluation via video EEG, and also included any randomized subjects who withdrew before the first the 24 hours of evaluation via video EEG, with reasons linked to lack or loss of efficacy (nonresponders for the primary efficacy end point).[22] In Study N132, main analysis was based on patients completing the titration period (in addition to responder analysis in all randomized patients).[19] Of the 5 trials using ITT analysis, although the ITT population was defined as analysis including all randomized patients who received at least 1 dose of the

study drug, this was technically an mITT population due to the requirement to have had at least 1 dose of study medication. Nonetheless, all randomized patients (except 1 patient in Study N166[23] and two patients in Study N1057) were included in the ITT populations (i.e., all randomized patients except 1 took at least 1 dose of the study drug). Therefore, it was unlikely to have an impact on the true ITT analysis.

One of the goals of the treatment of epilepsy is to maintain or restore HRQoL.[8] The QOLIE-31 was reportedly assessed in 3 trials, (N132, [19] N166,[23] and N1057 [24]) but, only 1 trial [19] reported the results. In Study N132, it was reported that overall HRQoL as measured by the QOLIE-31 questionnaire showed no significant effect but there was improvement in 3 of the 7 items: seizure worry, cognitive functioning, and overall quality of life.[19] Overall, there were lack of HRQoL data reported in the included trials.

External Validity

None of the trials included in the summary of clinical evidence provided by the sponsor were conducted using the formulation of the product under review (pdp-levETIRAcetam), which is acceptable for dugs reviewed through Health Canada's Submissions Relying on Third-Party Data pathway. Of the 7 included pivotal trials, only 1 trial (N1009)[22] was conducted using the levetiracetam oral solution (Keppra oral solution, UCB),[16] but this study was only 5 days in duration and included only pediatric patients.[22]

No direct comparative clinical trials were included in the sponsor's submission that compared levetiracetam oral solution with levetiracetam tablets. To fill this evidence gap, the sponsor provided bioequivalence[30] and physiochemistry test data.[14]

Of the 7 included pivotal trials, only 1 of the studies (N159)[21] included study sites in Canada. Most of the studies were conducted in throughout Europe, Central America, and the US, where treatment practice may differ from Canada. Nonetheless, the clinical expert consulted by CADTH for this review confirmed that the baseline demographic and disease characteristics were generally representative of Canadian patients with epilepsy.

As detailed in Table 8 across the treatment arms, in the 2 trials in the pediatric population,[21,22] a total of 69.3% to 78.4% of patients had tried at least 2 AEDs prior to study entry, which was aligned with patients seen in Canadian settings. Such information (the number of prior AEDs) was not provided for the trials in adults [18-20] or in the 2 studies in a mixed population of pediatric and adult patients.[23,24] This may have an impact on the generalizability of the trial results to patients who have not a similar degree of previous treatment with other AEDs (i.e., not considered to be as refractory to treatment or those patients who has tried ≥ 3 prior AEDs who were considered more refractory and therefore more difficult to treat than a less AED-experienced patient population).

In addition, patients older than 70 years were not included; therefore, whether the findings of the trials can be generalized to the geriatric population (i.e., age > 70 years) remains uncertain.

Furthermore, although the studies were only 12 weeks to 24 weeks in duration and there was lack of long-term evidence included in the sponsor's summary, levetiracetam has been available for over 10 years and its efficacy and safety profile is well established.

Despite the various generalizability issues discussed above, the clinical expert consulted for this review indicated that the baseline demographic and disease characteristics of the

patients enrolled in the 7 trials summarized by the sponsor are representative of patients with refractory epilepsy seen in clinical practice in Canada.

No comparative evidence of levetiracetam versus any other AEDs was included in the sponsor's summary of the clinical evidence. However, according to the expert consulted by CADTH for this review, it is generally accepted that all AEDs are of similar efficacy, but levetiracetam appears to be associated with an improved tolerability. Furthermore, the clinical expert consulted in the review indicated that this lack of comparative data would be unlikely to influence prescribing of levetiracetam oral solution.

Sponsor's Summary of the Cost Information

Table 18: Sponsor's Submitted Cost Comparison Table

Generic name (brand name)	Strength	Dosage form	Price ($)	Recommended dosage regimen[a]	Annual drug cost ($)[b]	Difference in annual cost ($)
pdp-LevETIRAcetam	100 mg/mL	Oral solution (300 mL)	244.2600	500 mg b.i.d.	2,931	—
Comparators						
Compounded oral solution	50 mg/mL	Oral suspension (600 mL)	51.9690	500 mg b.i.d.	623	+2,307

b.i.d. = twice a day.

Note: The cost of 30,000 mg compounded levetiracetam is derived from 60 of the 500 mg tablets and 600 mL of dissolution vehicles (300 mL Ora-Blend and 300 mL Ora-Sweet). Cost was determined by applying the cost of compounding the same amount of compounded levetiracetam tablets that is in a bottle of levetiracetam oral solution (30,000 mg). The cost table does not consider provincial dispensing fees, compounding fees, or pharmacy mark-up fees.

[a] Dosage obtained from pdp-levETIRAcetam product monograph.

[b] pdp-levETIRAcetam sponsor list price (July 2020).

Source: Ontario Drug Benefit Formulary (accessed May 2020) for the cost of levetiracetam 500 mg tablets and the Quebec Association of Proprietor Pharmacists (AQPP) drug list (accessed 2019) for the costs of Ora-Sweet and Ora-Blend dissolution vehicles.

The sponsor's submitted cost comparison presents the difference in treatment costs for different forms of the drug levetiracetam, as an adjunctive therapy for the treatment of epilepsy. The eligible patient population according to the Health Canada indication includes adult patients who are not satisfactorily controlled by conventional therapy and pediatric patients with seizures that meet the criteria outlined in Table 1. This cost comparison was undertaken from the perspective of the Canadian public drug plans and considered drug acquisition costs only. Provincial dispensing fees, compounding fees, or pharmacy mark-up fees were not considered.

Levetiracetam oral solution (100 mg/mL) is a new formulation of levetiracetam and is currently under review for the same indication as levetiracetam tablets in the adult population. Additionally, levetiracetam oral solution is under review for indications in pediatric patients. As part of the sponsor's submission, they assumed that levetiracetam oral solution would primarily replace the pharmacy-compounded suspension. The sponsor-submitted price of the oral solution is $244.26 per 300 mL bottle, for a total annual cost of $2,931 based on a dose of 1,000 mg daily, assuming that 12 bottles of oral solution would be dispensed annually. The sponsor assumed levetiracetam compounded suspension is produced by crushing 60 tablets of 500 mg levetiracetam into 300 mL of Ora-Sweet and 300 mL of Ora-Plus (i.e., 50 mg/mL).[31] The cost per 500 mg levetiracetam tablet is $0.3911 in the majority of participating jurisdictions, and the cost per mL of Ora-Sweet and Ora-Plus is $0.0507 and $0.0443, respectively. The cost of the compounded suspension was estimated to be approximately $51.97 per 600 mL (50 mg/mL), resulting in annual costs of $624 at a recommended dosage of 1,000 mg daily. The introduction of levetiracetam oral solution would be associated with an increased annual cost of $2,307 per patient compared to the compounded suspension.

CADTH's Critical Appraisal of the Cost Information

- **Variability in formulary prices for levetiracetam tablets:** The sponsor assumed that the pharmacy-compounded suspension would be produced using 500 mg tablets. For all provinces, including the Non-Insured Health Benefits Program, the cost per 500 mg tablet

of levetiracetam was $0.391; in Newfoundland and Labrador and British Columbia, the cost is higher at $0.426 and $0.422, respectively.

- **Uncertainty in equivalent dosing:** As mentioned in the bioequivalence section of the report, bioequivalence data submitted by the sponsor for 100 mg/mL levetiracetam oral solution was based on the 750 mg levetiracetam tablets to inform efficacy and safety.[30] But the sponsor assumes the pharmacy-compounded suspension would only be made using 500 mg tablets. 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.
- Sponsor only considered adult/adolescent dosing: The submitted Health Canada indication also recommends levetiracetam oral solution for children and infants with partial onset, myoclonic, and PGTC seizures.[9] The recommended daily dose of levetiracetam oral solution ranges from 7 mg/kg to 21 mg/kg twice daily for infants, 10 mg/kg to 30 mg/kg twice daily for adolescents, and 500 mg to 1,500 mg twice daily for adults weighing 50 kg or more. This wide range of dosages leads to highly variable annual costs. The sponsor only considered the recommended adult dose of 1,000 mg per day in their analysis.

Additional limitations were identified, but were not considered to be key limitations:

- **Sponsor did not include all relevant comparators according to the Health Canada indication:** Based on feedback from the clinical expert consulted by CADTH and the Ontario Epilepsy Guidelines[32], there are multiple comparators that could be considered as alternative treatment options based on the submitted Health Canada indications for levetiracetam oral solution (as seen in Table 19). Only brivaracetam, eslicarbazepine, and phenobarbital are more expensive than levetiracetam oral solution. For the other comparators, price reductions of up to 99% for levetiracetam oral solution would be required to match the least expensive comparators. However, as levetiracetam is well established in the market, the clinical expert consulted by CADTH confirmed that the oral solution would likely only replace the pharmacy-compounded suspension of levetiracetam.

CADTH Reanalyses

CADTH identified variations in publicly available prices across the jurisdictions for levetiracetam 500 mg tablets and explored the impact of this variation on the overall compounded suspension cost. The annual costs per 600 mL bottle of compounded suspension for the majority of public drug programs was $632 ($51.97 per bottle), with annual costs ranging between $655 in British Columbia ($53.84 per bottle) to $658 ($54.08 per bottle) in Newfoundland and Labrador. This may lead to incremental annual costs for the oral solution of $23 and $26 when compared to the original compounded suspension, respectively.

Based on the assumption of bioequivalence with 750 mg tablets and uncertainty of which tablet strength is used for compounding, CADTH explored the use of higher strength tablets to make the pharmacy-compounded suspension. For the 750 mg tablet, a price of $0.5416 was used and for the 1,000 mg tablet the cost was $0.7221.[33] In both cases this resulted in a cost per 600 mL bottle of suspension of $50.16, a minor drug price decrease (–3.5%) when compared to the compounded suspension made with 500 mg tablets. The annual cost for a compounded suspension made with 750 mg tablets is $610, leading to a reduced annual cost of $22 when compared to the compounded suspension using 500 mg tablets.

CADTH considered that the introduction of levetiracetam oral solution would result in less compounding fees for drug plans as the compounded suspension would be replaced by this treatment. Compounding fees across the jurisdictions ranged from $5.92 to $30.00 per claim,[34,35] resulting in increased annual costs of $704 to $997 for the compounded suspension. The annual difference in costs between levetiracetam oral solution and the compounded suspensions ranged from $1,975 to $2,268, indicating that the oral solution is more expensive even when accounting for costs offset by compounding fees.

Overall, the levetiracetam oral solution represents an approximately 10.4-fold and 4.7-fold increase in drug costs for public drug plans compared to the tablets and compounded suspension, respectively. Levetiracetam oral solution is likely to result in increased expenditures to the public drug plans due to the higher price per mg of the new formulation. To be considered cost-neutral when compared to levetiracetam tablets, the price of the oral solution would need to be reduced by 90.4% (Table 19). To be considered cost-neutral compared to the pharmacy-compounded suspension, the submitted price of levetiracetam oral solution would require a price reduction of 78.7%.

Table 19: CADTH Cost Comparison Table – New Formulation of Levetiracetam

Drug/comparator	Unit strength	Dosage form	Unit price ($)	Population	Recommended daily use	Average annual drug cost ($)	Relative difference in annual drug costs ($) compared to new formulation
New formulation							
Levetiracetam oral solution 100 mg/mL	**300 mL bottle**	**Oral solution**	**244.2600[a]**	**Adult/adolescent (age 12 years to 17 years and ≥ 50 kg)**	**500 mg twice daily**	**2,972**	**—**
				Pediatric (age 0 to 17 years and < 50 kg)	**10 mg/kg to 30 mg/kg twice daily**	**1,783 to 5,349[b]**	**—**
				Infant (age 1 month to 6 months)	**7 mg/kg to 21 mg/kg twice daily**	**135 to 955[b]**	**—**
				Maximum dose	**1,500 mg twice daily**	**8,915**	**—**
Reference formulation							
Levetiracetam compounded suspension 50 mg/mL	600 mL bottle (final product)	Oral suspension	51.9660[c]	Adult/adolescent (aged 12 years to 17 years and ≥ 50 kg)	500 mg twice daily[d]	632	–79% (–$2,339)
				Pediatric (age 0 to 17 years and < 50 kg)	10 mg/kg to 30 mg/kg twice daily[d]	379 to 1,138[b]	–79% (–$1,404 to –$4,211)
				Infant (age 1 month to 6 months)	7 mg/kg to 21 mg/kg twice daily[d]	29 to 203[b]	–79% (–$106 to –$752)
				Maximum dose	1,500 mg twice daily[d]	1,897	–79% (–$7,019)
Levetiracetam tablet	500 mg	Tablet	0.3911	NA	NA	NA	NA
Ora-Plus suspension vehicle	300 mL	Bottle	15.2100[e]	NA	NA	NA	NA

Drug/comparator	Unit strength	Dosage form	Unit price ($)	Population	Recommended daily use	Average annual drug cost ($)	Relative difference in annual drug costs ($) compared to new formulation
Ora-Sweet suspension vehicle	300 mL	Bottle	13.2900[e]	NA	NA	NA	NA

NA = not applicable.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed September 2020)[33] unless otherwise indicated and do not include dispensing fees. Annual cost calculations based on 365 days per year. Dosages are from each product's respective monograph, unless otherwise stated.

[a] Sponsor's submitted price.[14]

[b] Annual drug costs based on average (50th percentile) weights for children aged 9.5 years (30 kg) and for infants aged 2 months to 6 months (3.3 kg to 7.7 kg) based on Canadian WHO growth charts.[36]

[c] The sponsor assumed the compounded solution is produced by crushing 60 tablets of 500 mg levetiracetam into 300 mL of Ora-Sweet and 300 mL of Ora-Plus. This was based on the study by Ensom et al. (2011) assessing the stability of extemporaneously compounded suspensions of levetiracetam.[31]

[d] Levetiracetam compounded suspension is used off-label in children and adults with dysphagia.

[e] Sponsor obtained prices using the Quebec Association of Proprietor Pharmacists (AQPP) drug list (accessed April 2020).

Table 20: CADTH Cost Comparison Table – Relevant Comparators for Levetiracetam

Drug/comparator	Unit strength	Dosage form	Unit price ($)	Recommended daily use	Average annual drug cost ($)	Relative difference (%) in annual drug costs ($) compared to new formulation
New formulation						
Levetiracetam oral solution 100 mg/mL	**300 mL bottle**	**Oral solution**	**244.2600[a] (0.8142/mL)**	**500 mg twice daily (adults only)**	**2,972**	**—**
Relevant comparators						
Levetiracetam (tablets)	250 mg 500 mg 750 mg 1,000 mg	Tablet	0.3210 0.3911 0.5416 0.7221	1,000 mg to 3,000 mg in 2 doses daily (adults only)	286 to 813	–73% (–$2,159) to –90% (–$2,686)
Brivaracetam	10 mg 25 mg 50 mg 75 mg 100 mg	Tablet Tablet Tablet Tablet Tablet	4.3200 4.3200 4.3200 4.3200 4.3200	50 mg to 200 mg in 2 doses daily (adults only)	3,154	6% ($182)

Drug/comparator	Unit strength	Dosage form	Unit price ($)	Recommended daily use	Average annual drug cost ($)	Relative difference (%) in annual drug costs ($) compared to new formulation
Carbamazepine	200 mg 400 mg	Tablet	0.0930 0.1859	800 mg to 1,200 mg daily	136 to 204	–93% (–$2,768) to –95% (–$2,836)
Clobazam	10 mg	Tablet	0.2197	40 mg to 80 mg daily	321 to 642	–78% (–$2,330) to –89% (–$2,651)
Eslicarbazepine	200 mg 400 mg 600 mg 800 mg	Tablet	9.8700 9.8700 9.8700 9.8700	800 mg to 1,200 mg daily	3,603 to 7,205	21% ($631) to 142% ($4,233)
Gabapentin	100 mg 300 mg 400 mg	Capsule	0.0416 0.1012 0.1206	900 mg to 1,800 mg daily	111 to 206	–93% (–$2,765) to –96% (–$2,861)
Lamotrigine	25 mg 100 mg 150 mg	Tablet	0.0698 0.2787 0.4107	200 mg to 400 mg daily	203 to 407	–86% (–$2,565) to –93% (–$2,768)
Oxcarbazepine	150 mg 300 mg 600 mg	Tablet	0.6209 0.9102 1.8204	1,200 mg daily	1,329	–55% (–$1,643)
Phenobarbital	15 mg 30 mg 60 mg 100 mg	Tablet Tablet Tablet Tablet	0.1399 0.1665 0.2257 0.3088	50 to 100 mg 2 or 3 times daily	113 to 338	–89% (–$2,634) to –96% (–$2,859)
	5 mg/mL	Oral solution	0.1424	50 to 100 mg 2 or 3 times daily[b]	1,040 to 3,119	–65% (–$1,932) to 5% ($147)
Phenytoin	125 mg/5 mL 30 mg/5 mL	Oral susp. Oral susp.	0.2140 0.2520	25 to 125 mg daily (susp.)	16 to 78	–97% (–$2,894) to –99% (–$2,956)
	100 mg	Capsule	0.0665	300 mg to 400 mg daily (capsule)	73 to 97	–97% (–$2,875) to –98% (–$2,899)
Primidone	125 mg 250 mg	Tablet	0.0564 0.0887	500 mg to 1,000 mg daily	65 to 130	–96% (–$2,842) to –98% (–$2,907)
Topiramate	25 mg 100 mg 200 mg	Tablet	0.2433 0.4583 0.6748	200 mg to 400 mg in 2 doses daily	335 to 493	–83% (–$2,479) to –89% (–$2,637)

Drug/comparator	Unit strength	Dosage form	Unit price ($)	Recommended daily use	Average annual drug cost ($)	Relative difference (%) in annual drug costs ($) compared to new formulation
Valproic acid	250 mg 500 mg 250 mg/5 mL	Capsule Capsule Oral solution	0.2905 0.6356 0.0653[c]	750 mg to 1,000 mg daily[d]	72 to 95	–97% (–$2,876) –98% (–$2,900)

susp = suspension.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed September 2020)[33] unless otherwise indicated and do not include dispensing fees. Annual cost calculations based on 365 days per year. Comparators were identified from the Ontario epilepsy guidelines.[32] Dosages are from each product's respective monograph, unless otherwise stated.

[a] Sponsor's submitted price.[14]

[b] The recommended dosing is based on adult patients receiving levetiracetam tablets as an anticonvulsant as a proxy given that no recommended dosage was provided for phenobarbital elixir.[37]

[c] British Columbia formulary (accessed September 2020).[38]

[d] Dosage obtained from myrxtx.ca.[39]

Issues for Consideration

- **Off-label use of levetiracetam:** Clinical experts consulted by CADTH indicated that levetiracetam is often prescribed beyond the approved indication (i.e., used off-label). Specifically, it was noted that levetiracetam is routinely used as first-line monotherapy based on a relatively favourable safety profile compared to other available treatments and is not exclusively used as adjunctive therapy.
- **Compounding fees:** While the introduction of levetiracetam oral solution will result in fewer compounding fees being incurred by public drug plans, this reduction in costs will not offset the increased cost of levetiracetam oral solution as compared to the compounded suspension.

Discussion

Summary of Available Evidence

The CADTH clinical review was based on a summary of clinical evidence provided by the sponsor and focused on the clinical studies that are referenced in the approved product monograph for pdp-levETIRAcetam.

All the evidence provided in the submission is based on third-party data using the levetiracetam tablet (Keppra), with the exception of Study N159 which used the Keppra oral solution. One bioequivalence study of the levetiracetam tablet versus the oral solution (Keppra tablet versus oral solution)[16] and 1 in vitro study of [redacted] were also summarized by the sponsor.

Overall, the body of evidence for the review included 7 trials:

- 3 trials (N051,[18] N132,[19] and N138[20]) were conducted in adult patients 16 years to 70 years of age with refractory partial onset epilepsy
- 2 trials (N159[21] and N1009[22]) were conducted in pediatric patients (aged 1 month to 16 years) with refractory partial onset epilepsy
- 2 trials (N166[23] and N1057[24]) were conducted in a mixed population of pediatric and adult patients (aged 4 years to 65 years) with refractory generalized myoclonic or generalized tonic-clonic epilepsy.

Of the 7 RCTs, 6 (N051, N132, N138, N159, N166, and N1057) were multi-centre, double-blind, parallel group, randomized, placebo-controlled, phase III trials and investigated the efficacy and safety of levetiracetam tablet (Keppra tablet, UCB) given as adjunctive therapy (i.e., added on to a background regimen of 1 to 3 AEDs) in patients 4 years old to 70 years old for the treatment of refractory epilepsy. Study N1009[22] was an RCT that investigated the levetiracetam oral solution (Keppra oral solution,100 mg/mL)[16] for the treatment of patients with refractory partial onset epilepsy who were 1 month of age to 4 years old.

The trials investigated different doses of levetiracetam (1,000 mg/day to 3,000 mg/day in adults and up to 60 mg/kg per day in children). The duration of the double-blind treatment period in studies N051, N132, N138, N159, N166, and N1057 was from 12 to 24 weeks; the duration of treatment in Study N1009 was 5 days. In 5 trials (N051,[18] N132,[19] N138,[20] N159,[21] and in N1057 [24]), the primary efficacy outcome was the change from baseline in reduction of the seizure frequency per week. In 2 trials (N1009[22] and N166[23]), the primary outcome was the proportion patients who achieved a 50% or greater reduction of seizure frequency (i.e., the responder) at the end of the trial.

Interpretation of Results

Efficacy

Studies in Adults (Aged 16 Years to 70 Years)

Overall, the 3 trials (N051, N132, and N138) [18-20] 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.

Studies in Children (Aged 1 Month to 16 Years)

Study N159[21] showed that adjunctive treatment with levetiracetam tablets resulted in greater reductions in total seizure frequency per week compared with placebo in pediatric patients aged 4 years to 16 years with partial onset seizures.

The other trial in pediatric patients, Study N1009,[22] was the only study included that investigated the levetiracetam oral solution (Keppra oral solution, UCB).[16] It was also the only study that was conducted in patients younger than 4 years of age. It was reported that a greater proportion of patients treated with levetiracetam achieved a 50% or greater reduction in seizure frequency from baseline compared to patients treated with placebo. According to the summary of clinical evidence submitted by the sponsor, due to the small sample size in each age group, it was not feasible to demonstrate statistically significant treatment effect within each age subgroup. The key limitation of this study was that the duration of treatment was only 5 days.

Studies Including a Mixed Population of Children and Adults (Aged 4 Years to 65 Years)

Study N166[23] included patients aged 12 years to 65 years with myoclonic seizures. A higher percentage of patients who received levetiracetam tablets as adjunctive treatment achieved the 50% responder rate group compared with the placebo group.

Study N1057[24] included patients 4 years to 65 years of age with generalized tonic-clonic seizures. A greater response in terms of the reduction of seizure frequency was observed in the levetiracetam 3,000 mg/day group than in the placebo group.[13] In terms of the proportion of patients who achieved a 50% or greater reduction of seizure frequency (i.e., the responder), a greater proportion of patients were considered responders than in placebo group. However, based on the information reported in Health Canada reviewer's report[13]:

> There was an issue with the age distribution in the trial. That is, 90% of the trial population was > 16 years. There were only 5 patients in the levetiracetam group between the ages of 12 to 16, 3 patients less than 12 years old, and only 1 patient less than 6 years old. Therefore, Health Canada has not accepted the lower age limit of 4 which was proposed by the sponsor, and instead has granted the indication for patients over 12 years old.

In both trials, N166 and N1057, the findings were limited by no subgroup analysis for either the adult or children population, respectively.

Overall, levetiracetam tablets (Keppra tablets, UCB)[15] used as adjunctive treatment were efficacious in reducing seizure frequency in adult patients (aged 16 years to 70 years) with partial onset, myoclonic, and PGTC seizures. Levetiracetam tablets used as adjunctive treatment was also efficacious in reducing seizure frequency in pediatric patients with partial onset and myoclonic seizures who were at least 12 years of age, and in patients with PGTC seizures who were at least 4 years of age. One study (N1009)[22] demonstrated that levetiracetam oral solution[16] used as adjunctive treatment was efficacious in reducing the seizure frequency in pediatric patients with partial onset seizures; however, this study was not conducted with the product under review. The clinical expert consulted for this review indicated that the clinical significance of the reduction of the seizure frequency depends on the baseline seizure frequency and that seizure free for a minimum of 3 times the interseizure interval or 12 months is considered a clinical meaningful response to the AEDs

treatment. In the Ontario guidelines, it is indicated that antiepileptic treatment might be discontinued after a minimum period of 1 year to 2 years of seizure freedom.[7]

Harms

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

Across the 7 included studies, the proportion of the patients that experienced at least 1 TEAE were largely similar between the levetiracetam and placebo arms, and appeared to be similar across the studies in adults and children. Overall, the most frequently reported TEAEs were somnolence, agitation, depression, nasopharyngitis, headache, fatigue, anorexia, and dizziness. The clinical expert consulted for this review indicated that the AEs reported in the included trials are aligned with what expected in clinical practice. That is, levetiracetam has a favourable side effect profile, but is known to cause psychiatric and behavioural effects.

The percentage of patients experiencing at least 1 SAE and most common SAEs were not available in the sponsor's summary of evidence for all of the studies. The same is true for the data presented regarding withdrawal due to AEs. Information pertaining to AEs 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 reactions, as well as anorexia and decreased appetite, which were more common in children than in adults.[9]

There were no deaths reported during the treatment periods of the all included trials except that in N132,[19] In Study N132, 2 deaths were reported. Of the 2 deaths, 1 patient died before randomization after having a severe seizure, which was attributed to the seizure disorder. The second death occurred in the placebo group.

Consideration must be given to the fact that patients were on concomitant background AED regimens which could have contributed to the safety and tolerability profile of levetiracetam. Despite this, levetiracetam appeared to be relatively well tolerated.

Cost

At an average daily dosage of 1,000 mg, the annual cost for levetiracetam oral solution is $2,972 (Table 19). This represents a 4.7-fold increase (additional $2,340 per patient annually) in drug costs compared to the compounded suspension it is intended to replace, and a 10.4-fold increase (additional $2,686 per patient annually) compared to levetiracetam tablets. In both cases, reimbursement of levetiracetam oral solution will result in increased drug expenditures for the public drug plans. While some of the increased cost would be offset by a small savings on compounding fees, at the submitted price, the sponsor is seeking a price premium for the oral solution form.

Compared to levetiracetam oral solution, annual expenditures for other drugs available for epilepsy range from a cost savings of $4,233 (eslicarbazepine) to increased costs of $2,956 (phenytoin) per patient.

Other Considerations

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 focused on the clinical studies that are referenced in the product monograph for pdp-levETIRAcetam. All the evidence provided in the submission is based on third-party data using the levetiracetam tablet (with the exception of Study N159). One bioequivalence study of the levetiracetam tablet versus the oral solution (Keppra tablet versus oral solution)[16] and 1 in vitro study of [redacted] were also summarized by the sponsor. In the Health Canada reviewer report, the following was indicated that:

> The tablet formulation of levetiracetam has been marketed globally since 1999, as Keppra (by UCB). Keppra tablets have been on the Canadian market since 2003. The oral formulations of Keppra have been approved by both FDA and EMA for > 10 years. The oral solution has had pediatric indication in both jurisdictions since 2005. Currently, the sole levetiracetam formulation on the Canadian market is that of tablet, as Keppra and various generics. Keppra tablets are approved only for adults (age 18 and over). The innovator sponsor, UCB, has chosen not to submit a marketing request in Canada for either of the solutions, nor for any pediatric indications.[13]

One evidence gap identified in this review is that none of the trials included in the summary of clinical evidence provided by the sponsor were conducted using the formulation of the product under review (pdp-levETIRAcetam). The 7 pivotal trials included in the sponsor's summary of the clinical evidence were conducted with levetiracetam tablets and oral solution developed and marketed by UCB. Further, there are no clinical trials comparing the efficacy and safety of levetiracetam oral solution to tablets. To fill this gap, the sponsor included information from a bioequivalence study conducted between the tablet and oral solution formulations of levetiracetam developed by UCB. Results of this study show that the 90% confidence limits of the geometric mean ratio of the 2 formulations for $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, and C_{max} were within the 80% to 125% range; therefore, the bioequivalence of the 2 formulations was established.[30] The sponsor also included results from an in vitro comparative analysis between [redacted] Results show that [redacted]

A topic deserving consideration is that the evidence provided for this review does not align with the current use of levetiracetam or anticipated use of levetiracetam oral solution. In the included trials, the levetiracetam tablets and oral solution were used as adjunctive treatment in patients who were inadequately controlled with other AEDs. The levetiracetam oral solution was approved by Health Canada in July 2019. The Health Canada approved indications[9] for levetiracetam oral solution are the following:

Adults: as adjunctive therapy in the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy

Pediatrics: as adjunctive therapy in the treatment of: partial onset seizures with or without secondary generalization in adolescents, children, and infants from 1 month of age with epilepsy, myoclonic seizures in adolescents from 12 years of age with JME, and PGTC seizures in adolescents from 12 years of age with idiopathic generalized epilepsy.

However, as indicated by the clinical expert consulted for this review, the use of levetiracetam in the trials does not align with how levetiracetam is used in clinical practice in Canada. This was acknowledged in a CADTH report (2011)[10] that "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."[10]

The clinical expert consulted by CADTH for this review indicated that in clinical practice, levetiracetam is considered an appropriate first-line treatment for epilepsy given its favourable side effect profile and broad spectrum efficacy. Levetiracetam tablets are used as an oral treatment for patients who are able to swallow pills. On some occasions they are crushed for making compounding suspension for people who cannot swallow pills. The clinical expert also indicated that it is common in clinical practice to use a compounded suspension from levetiracetam tablet for those patients who have swallowing difficulties, such as for children under 6 years of age. The clinical expert indicated that the anticipated place in therapy for the oral solution is mainly in young children who cannot swallow tablets and that it may be used as a first-line monotherapy.

Levetiracetam tablets are currently listed on most public drug plan formularies and many plans have also listed the levetiracetam compounded suspension (50 mg/mL) either as a as full benefit or as restricted benefit with specified criteria (e.g., special authorization, exception drug status, or limited use benefit).

Conclusions

Based on the summary of clinical evidence submitted by the sponsor, compared with placebo, levetiracetam tablets (Keppra tablets, UCB) used as adjunctive treatment demonstrated a greater reduction in seizure frequency in adult (aged 16 years to 70 years) and pediatric (aged 4 years to 16 years) patients with refractory epilepsy. In addition, a greater proportion of patients treated with levetiracetam were considered responders (i.e., achieved a 50% or greater reduction of seizure frequency) than in the placebo group. In 1 study conducted in children aged 1 month to less than 4 years, adjunctive treatment with levetiracetam oral solution (Keppra oral solution, UCB) resulted in a greater proportion of patients achieving a 50% or greater reduction of seizure frequency than in the placebo group.

The sponsor's summary of evidence was based on third-party data and only published studies were available. Despite the lack of methodological detail, the studies appear to be well conducted. Further, the clinical expert consulted for this review indicated that the findings of the clinical efficacy and AEs reported in the included trials were aligned with what would be expected in Canadian clinical practice.

At the submitted price based on the recommended daily dose of 1,000 mg per day, levetiracetam oral solution was associated with increased annual expenditures of $2,340 per patient when compared with the compounded suspension and $2,686 per patient when compared to levetiracetam oral tablets. However, there was variability in the list prices for levetiracetam among jurisdictions and the recommended dosing according to each patient population that influence annual cost estimates.

Appendix 1: Reimbursement Status for Comparators

The comparator for pdp-levETIRAcetam is the oral suspension of levetiracetam prepared in pharmacies. Pdp-levETIRAcetam is a commercialized formulation of an extemporaneous formulation commonly used in Canadian children without an approved pediatric indication.

When a commercialized drug is available, Health Canada and provincial college of pharmacist regulations indicate that compounding should stop.

Currently, given that pdp-levETIRAcetam oral solution has been available since May 2020, it is likely that the compounding of levetiracetam oral suspension is not reimbursed anymore, except under exceptional access in some provinces.

Appendix 2: Submitted Budget Impact Analysis and CADTH Appraisal

Key Take-Aways of the Budget Impact Analysis

- CADTH identified the market size of levetiracetam oral solution as being underestimated in the sponsor's base case. Based on CADTH reanalyses, similar to the sponsor's findings, reimbursement of levetiracetam oral solution results in an increase in budget for public drug programs, although CADTH suggests that the 3-year budget impact would be higher than estimated by the sponsor at $17,110,610.

Summary of Sponsor's Budget Impact Analysis

The submitted budget impact analysis (BIA) assessed the introduction of levetiracetam oral solution as an adjunctive therapy for the treatment of epilepsy in adult and pediatric patients. This claims-based BIA was conducted from the perspective of Canadian drug plans over a 3-year time horizon (January 2021 to December 2023, with 2020 as a base year). The sponsor's base case considered drug acquisition costs, provincial dispensing fees, and pharmacy mark-up fees, while compounding fees were not considered.

The reference case scenario in which levetiracetam oral solution is not available included 2 treatments: levetiracetam tablets which made up the majority of the market share (95%), and pharmacy-compounded levetiracetam oral suspension supplied by local pharmacies (5%). In the new drug scenario, it was assumed that all the market share for the compounded oral suspension would be displaced by levetiracetam oral solution, with the market share for levetiracetam tablets remaining unchanged. The market share estimate for the proportion of patients requiring an oral solution or compounded suspension was 5% in both scenarios. This estimate was based on a number of assumptions: 100% of infants under the age of 6 would take the oral solution, 16% of patients aged 6 to 17 were unable to swallow tablets and would thus take the oral solution,[40,41] and 3.0% of adults and elderly patients experienced dysphagia and would also take the oral solution.[42] Key inputs to the BIA are documented in Table 21.

Table 21: Summary of Key Model Parameters

Parameter	Sponsor's estimate (reported as year 1/year 2/year 3 if appropriate)
Estimated market size	
Number of levetiracetam tablets in 2019	26,636,323
Mean annual growth of Canadian population (%)	1.43[14]
Number of levetiracetam tablets in year 1, 2, and 3	27,429,602/27,835,449/28,247,560
Market uptake (3 years)	
Uptake (reference scenario) Levetiracetam tablet (%) Levetiracetam compounded suspension (%)	 95/95/95 5/5/5
Uptake (new drug scenario)[a] Levetiracetam tablet (%) Levetiracetam compounded suspension (%) Levetiracetam oral solution (%)	 95/95/95 0/0/0 5/5/5

Parameter	Sponsor's estimate (reported as year 1/year 2/year 3 if appropriate)
Cost of treatment (per patient)	
Cost of treatment over 1 year (1000 mg/day) Levetiracetam oral solution ($) Levetiracetam compounded suspension ($) Levetiracetam tablet ($)	 2,971.83 632.25 285.50

[a] The sponsor assumed that levetiracetam oral solution would entirely replace the market share of levetiracetam compounded suspension in the new drug scenario.

Summary of the Sponsor's BIA Results

According to the sponsor's submitted analysis, the estimated incremental budget impact of reimbursing levetiracetam oral solution for the treatment of epilepsy in adult and pediatric patients was $4,489,058 in year 1, $4,555,200 in year 2, and $4,622,363 in year 3, for a 3-year total budget impact of $13,666,621.

CADTH Appraisal of the Sponsor's BIA

CADTH identified the following key limitations to the sponsor's analysis that have notable implications on the results of the BIA.

- Market share for oral solution likely underestimated: The expected market share of levetiracetam oral solution of 5% is based on assumptions about the number of children and adults who are unable to swallow pills; however, this drug could be used by any patient meeting the Health Canada indication.
- The clinical expert consulted by CADTH highlighted the uncertainty in the evidence base regarding the proportion of children unable to swallow pills. The expert further noted that the estimate of 5% used by the sponsor for levetiracetam oral solution uptake likely did not consider patients fed via a gastrostomy tube, who would likely receive levetiracetam as an oral solution. Estimates of the proportion of children and adolescent patients with epilepsy who are fed from a gastrostomy tube range from 15.6% to 22.9%,[43-45] and these patients would not have been eligible for the studies cited by the sponsor to estimate swallowing difficulty.[40,41] In addition, the clinical expert noted that in rare cases levetiracetam oral solution might replace some use of levetiracetam tablets, in rural or remote communities where compounding is not routinely performed. Patients in those situations who receive a liquid formulation of the drug would instead be receiving levetiracetam tablets in the reference scenario.
- Both of these considerations suggest that the market share for oral solution is likely underestimated. Given that levetiracetam oral solution is more expensive than the tablets on an annual basis, the resulting budget impact is also likely underestimated.

As part of the base case, CADTH assumed that 22.9% of children and adolescent patients would be fed via gastrostomy tube and were therefore likely to receive levetiracetam oral solution.[44] This proportion was added into the weighted average used to derive the 5% estimate, resulting in a final market share for levetiracetam oral solution of 6.26%. This market size is likely still underestimated due to the lack of data to inform the proportion of adult patients fed via gastrostomy tubes.

CADTH conducted exploratory analyses in which the market share of levetiracetam oral solution versus tablets was estimated by using IQVIA Pharmastat public claims data from April 2019 to March 2020 for carbamazepine, oxcarbazepine, and valproic acid.[46] These 3 drugs were validated by the clinical expert consulted by CADTH as appropriate representations for levetiracetam in that they would likely be prescribed in similar situations.

For carbamazepine, oxcarbazepine, and valproic acid the market shares for the oral solution versus tablet formulation were 7.18%, 4.35%, and 22.13%, respectively.

- **Pharmacy-compounded suspension is only assumed to be made with 500 mg tablets:** The sponsor assumed the levetiracetam compounded suspension would only be made using 500 mg tablets, which have a higher cost per mg than the 750 mg tablets. This approach aligns with a recent study in Canada evaluating the stability of extemporaneously compounded suspensions of levetiracetam which utilized 500 mg tablets which were suspended in a 1:1 solution of Ora-Sweet and Ora-Plus.[31] However, the bioequivalence data submitted by the sponsor based on the study by Coupez et al. was used to compare 100 mg/mL oral solution and 750 mg tablets.[30] Therefore, there is uncertainty regarding the use of 500 mg tablet treatments costs. When using the 750 mg tablet costs, the compounded suspension has a price of $50.16 versus $51.97 for 500 mg tablets.
    - CADTH explored the impact on the budget when the compounded suspension was assumed to be made using 750 mg tablets in a scenario analysis.
- **Simplistic assumption regarding daily levetiracetam dose:** The sponsor's claims-based approach did not account for the various recommended doses in the different types of seizures. Based on the patient's age and seizure type, the recommended daily dose of levetiracetam can range from 14 mg/kg to 3,000 mg. In the submitted analysis, the sponsor indirectly assumed a daily dose of 1,000 mg for all patients and used this dosage to calculate costs. This assumption oversimplifies the spectrum of dosing regimens available for this drug. CADTH considered it more appropriate to model the budget impact based on the various Health Canada indications and the respective recommended dosing regimens.
    - CADTH was unable to address this limitation without structural changes to the submitted BIA.

Additional limitations were identified but were not considered to be key limitations.

- **Overestimation of the total market size:** The claims data submitted by the sponsor indicated that 16.65% of all levetiracetam claims were for the 250 mg tablets, 71.05% were for 500 mg tablets, 12.30% were for 750 mg tablets, and 0.00% were for 1,000 mg tablets. To estimate the total market size in their base case, the sponsor assumed that all claimed units of levetiracetam were of the 500 mg variety, and thus had the potential to be used in the compounded suspension. The total market size, therefore, would have been overestimated if only the 500 mg tablets are used for compounding a suspension as suggested by the sponsor; however, this assumption would likely bias results against levetiracetam oral solution.[31]
    - The sponsor-submitted model did not allow for significant revisions to the total market size and CADTH was unable to address this assumption.
- **Off-label use of levetiracetam:** The clinical expert consulted by CADTH indicated that levetiracetam is often prescribed outside the purview of the health indication (i.e., off-label use). The claims-based approach utilized by the sponsor may underestimate the levetiracetam market size, and therefore underestimate the 3-year budget impact, as reported claims are likely not inclusive of off-label use.
    - CADTH was unable to address this limitation as claims data likely do not account for off-label use.
- **Sponsor did not include all relevant comparators:** The sponsor included in their BIA the various forms of levetiracetam: oral solution, compounded suspension, and tablets. No other comparators were included, despite there being the potential for levetiracetam oral solution to replace any AED.

- Clinical experts consulted by CADTH stated that it was unlikely levetiracetam oral solution would replace other treatments outside of the compounded suspension. Therefore, the exclusion of these treatments is unlikely to affect the budget impact; however, if public drug plans reimburse other products for epilepsy, the current analysis and corresponding results may not be reflective of their jurisdiction.

CADTH Reanalyses of the Budget Impact Analysis

CADTH considered the proportion of children and adolescent patients fed via gastrostomy tube as relevant to the estimate of market size and changed the proportion of patients unable to swallow tablets as part of the base case (Table 22). CADTH was unable to address the limitations surrounding off-label use of levetiracetam and the daily dose of the oral solution by indication.

Table 22: CADTH Revisions to the Submitted Budget Impact Analysis

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
None		
Changes to derive the CADTH base case		
Increased market share assumption for levetiracetam oral solution by considering patients fed via gastrostomy tube (**CADTH base case**)	• Levetiracetam compounded suspension market share: 5% • Levetiracetam oral solution market share: 5%	• Levetiracetam compounded suspension market share: 6.26% • Levetiracetam oral solution market share: 6.26%

The CADTH reanalysis is presented in summary format in Table 23. Based on the CADTH base case, the expected budget impact for reimbursing levetiracetam oral solution for patients with epilepsy is expected to be $5,620,301 in year 1, $5,703,110 in year 2, and $5,787,199 in year 3, resulting in a 3-year budget impact of $17,110,610.

CADTH performed a scenario analysis involving the assumption that the compounded suspension is prepared using 750 mg tablets, resulting in a cost per 600 mL bottle of $50.16. The resulting 3-year budget impact was $18,901,909.

As an exploratory analysis, CADTH estimated the market share of levetiracetam oral solution using carbamazepine, oxcarbazepine, and valproic acid as representations of the expected market share uptake of oral solutions, with the resulting 3-year BIA ranging from $11,889,960 to $60,488,466. CADTH recognizes the uncertainty associated with using claims data, in that these data represent all claims and not necessarily those for only epilepsy. Furthermore, there is uncertainty regarding the proportion of claims utilized by children and adults. However, CADTH found the BIA to be highly influenced by market share assumptions.

Table 23: Summary of the Budget Impact Analysis – CADTH Base Case

Stepped analysis	3-year total
Submitted base case	$13,666,621
CADTH reanalysis 1: increased market share of levetiracetam oral solution	$17,110,610
CADTH base case	**$17,110,610**

Note: the submitted analysis is based on the publicly available prices of the comparator treatments.

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