NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Levetiracetam Lupin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Levetiracetam Lupin film-coated tablets are available in strengths of 250 mg, 500 mg, 750 mg and 1000 mg.

Excipients with known effect (750 mg only): Each film-coated tablet contains 0.13 mg of E110 Sunset yellow FCF.

For the full list of excipients, see **Section 6.1 List of Excipients**.

3 PHARMACEUTICAL FORM

Levetiracetam Lupin 250 mg: Blue, oblong-shaped, biconvex, film-coated tablet debossed with '250' on one side and score line on the other side.

Levetiracetam Lupin 500 mg: Yellow, oblong-shaped, biconvex, film-coated tablet debossed with '500' on one side and score line on the other side.

Levetiracetam Lupin 750 mg: Peach-coloured, oblong-shaped, biconvex, film-coated tablet debossed with '750' on one side and score line on the other side.

Levetiracetam Lupin 1000 mg: White to off-white, oblong-shaped, biconvex, film-coated tablet debossed with '1000' on one side and score line on the other side.

The tablets can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Levetiracetam Lupin tablets are indicated for:

- use in epileptic patients aged 4 years and older, initially as add-on therapy, in the treatment of partial onset seizures with or without secondary generalisation.
- monotherapy in the treatment of partial onset seizures, with or without secondary generalisation, in patients from 16 years of age with newly diagnosed epilepsy.
- add-on therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy (JME).
- add-on therapy in the treatment of primary generalised tonic-clonic (PGTC) seizures in adults and children from 4 years of age with idiopathic generalised epilepsy (IGE).

4.2 Dose and Method of Administration

Levetiracetam treatment can be given either through oral or intravenous administration. Converting from oral to intravenous or intravenous to oral administration does not require titration and, in this case, the total dosage prescribed and the frequency of levetiracetam administration should be continued. Please note that levetiracetam tablets should not be used for intravenous administration.

Levetiracetam Lupin tablets must be taken orally, with or without food, and swallowed with liquid. The film-coated tablets may be taken with or without food. The daily dose is administered in two equal dose amounts.

Monotherapy

The recommended starting dose is 250 mg twice daily which should be increased to an initial therapeutic dose of 500 mg twice daily after 2 weeks. The dose can be further increased by 250 mg twice daily every two weeks depending upon the clinical response. The maximum dose is 1500 mg twice daily.

Add-on Therapy

Adults (≥18 years of age) and Adolescents (aged 12-17 years of age) Weighing 50 kg or More

As adjunctive therapy, the therapeutic dose is 500 mg twice daily. This dose can be started on the first day of treatment.

Depending upon the clinical response and tolerance, the daily dose can be increased up to 1500 mg twice daily. Dose changes can be made in 500 mg twice daily increments or decrements every 2 to 4 weeks.

When satisfactory control of seizures has been attained, monotherapy with levetiracetam may be envisaged by progressively decreasing and withdrawing the concomitant anti-epileptic medication.

Elderly (65 years and older)

Adjustment of the dose is recommended in the elderly if they have compromised renal function (see **Patients With Renal Impairment – Table 2**).

Children (aged 4 to 11 years of age) and Adolescents (aged 12-17 years of age) Weighing Less Than 50 kg

The initial therapeutic dose is 10 mg/kg twice daily (see **Table 1**).

Depending on the clinical response and tolerance, the daily dose can be increased up to 60 mg/kg daily (in two 30 mg/kg doses). Dose changes can be made in 10 mg/kg twice daily dose increments or decrements every two weeks. The lowest effective dose should be used.

For children over 50 kg the dosage is the same as in adults.

According to weight and dose, the physician should prescribe the most appropriate strength.

Table 1: Recommended dosing in children aged 6 years and older

Weight	Starting Dose: 10 mg/kg twice daily	Maximum Dose: 30 mg/kg twice daily
15 kg[(1)]	150 mg (1.5 mL) twice daily	450 mg (4.5 mL) twice daily
20 kg[(1)]	200 mg (2.0 mL) twice daily	600 mg (6.0 mL) twice daily
25 kg	250 mg (2.5 mL) twice daily	750 mg (7.5 mL) twice daily
From 50 kg[(2)]	500 mg (5.0 mL) twice daily	1500 mg (15 mL) twice daily

(1) Children 20 kg or less should preferably start the treatment with oral solution.
(2) Dosage in children and adolescents 50 kg or more is the same as in adults.

Infants and Children Less Than 4 Years of Age

There is insufficient data to recommend the use of levetiracetam in children under 4 years of age.

Patients With Renal Impairment

Dose adaptation may be required for the administration of levetiracetam in patients with renal impairment.

Table 2: Dosage schedule based on renal function (adults)

Group	Creatinine Clearance (mL/min)	Frequency (daily)	Dosage (mg)
End-stage renal disease patients undergoing dialysis (a 750 mg loading dose is recommended on the first day of treatment with levetiracetam)	–	Once (following dialysis, a 250 mg to 500 mg supplemental dose is recommended)	500 to 1,000
Severe	<30	Twice	250 to 500
Moderate	30-49	Twice	250 to 750
Mild	50-79	Twice	500 to 1,000
Normal	>80	Twice	500 to 1,500

In determining dosage, an estimate of the patient's creatinine clearance (CLcr) in mL/min is needed. The CLcr in mL/min may be estimated from serum creatinine (mg/dL) using the following formula:

$$CLCr = \frac{[\text{weight (kg)}] \times 140 - \text{age (years)}]}{0.8136 \times \text{serum creatinine (mg/dL)}} \quad (\times 0.85 \text{ for women})$$

Using (BSA) body surface area the CLcr is adjusted using the following formulation:

$$CLCr\ (mL/min/1.73\ m^2) = \frac{1.73 \times CLcr\ (mL/min)}{BSA\ subject\ (m^2)}$$

For children with renal impairment, levetiracetam clearance is related to renal function, therefore dosage needs to be adjusted based on renal function. This advice is recommended based on an adult impaired renal function study.

Patients With Hepatic Impairment

In patients with mild or moderate hepatic impairment, no dose adjustment is needed. In patients with severe hepatic impairment when the CLcr is <60 mL/min/1.73 m^2, a 50% reduction of the daily maintenance dose is recommended. This is because the creatinine clearance may underestimate the renal insufficiency.

4.3 Contraindications

This product should not be administered to patients who have known hypersensitivity to levetiracetam or other pyrrolidone derivatives or any of the inactive ingredients in levetiracetam tablets or oral solution (see **Section 6.1 List of Excipients**).

4.4 Special Warnings and Precautions for Use

Levetiracetam, in accordance with current clinical practice, should be withdrawn gradually if it has to be discontinued.

Due to its complete and linear absorption, plasma levels can be predicted from the oral dose of levetiracetam expressed as mg/kg bodyweight. There is no need therefore for plasma level monitoring of levetiracetam.

Suicidal Behaviour and Ideation

Anti-epileptic drugs (AEDs), including levetiracetam, increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive-therapy) of 11 different AEDs showed that patients randomised to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behaviour compared to patients randomised to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behaviour or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behaviour for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behaviour with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behaviour beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behaviour was generally consistent among drugs in the data analysed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analysed. **Table 3** shows absolute and relative risk by indication for all evaluated AEDs.

Table 3 Risk by indication for anti-epileptic drugs (AEDs) in the pooled analysis indication

Indication	Placebo Patients with Events per 1,000 Patients	Drug Patients with Events per 1,000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Event per 1,000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behaviour was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing levetiracetam or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviour. Should suicidal thoughts and behaviour emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behaviour and should be advised of the need to be alert for the emergence of worsening of the signs and symptoms of depression, any unusual changes in mood or behaviour, or the emergence of suicidal thoughts, behaviour, or thoughts about self-harm. Behaviours of concern should be reported immediately to the treating doctor.

Alcohol

There is no data available on the interaction of alcohol with levetiracetam.

Blood Cell Count

Reports of blood cell counts that were reduced, for example, agranulocytosis, leucopenia, neutropenia, pancytopenia and thrombocytopenia, have been found in association with administration of levetiracetam. It is recommended that complete blood cell counts are completed in individuals experiencing coagulation disorders, infections that are recurring, significant weakness or pyrexia (see **Section 4.8 Undesirable Effects**).

Use in Hepatic Impairment

See **Section 4.2 Dose and Method of Administration** and **Section 5.2 Pharmacokinetic Properties**.

Use in Renal Impairment

Monitoring of renal function in severe hepatic impaired patients is recommended before dose selection. The administration of levetiracetam to patients with renal impairment may require dose adaptation (see **Section 4.2 Dose and Method of Administration**).

Use in the Elderly

See **Section 4.2 Dose and Method of Administration** and **Section 5.2 Pharmacokinetic Properties**.

Paediatric Use

There is no evidence or data to recommend the use of levetiracetam treatment in children younger than 4 years old.

Effects on Laboratory Tests

No information available.

4.5 Interactions with Other Medicines and Other Forms of Interactions

Levetiracetam did not cause enzyme induction in human culture hepatocytes. Levetiracetam and its major metabolite (ucb L057) *in vitro*, do not inhibit the major human liver cytochrome P450 isoforms, epoxide hydroxylase and glucuronyl transferase, activities.

The renal clearance of the major metabolite (ucb L057) has been shown to be inhibited by probenecid (500 mg four times daily) although levetiracetam is not inhibited by probenecid. The concentration of ucb L057 remains low nevertheless. It is expected the renal clearance of the metabolite ucb L057 could also be reduced by other drugs that are excreted by active tubular secretion. The effect of probenicid interacting with levetiracetam was not studied and the effect of levetiracetam on other actively secreted drugs, eg. methotrexate, NSAIDs and sulphonamides, is not known.

In adults, pre-marketing data from clinical studies conducted indicate that levetiracetam did not influence the following existing anti-epileptic medicines (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) serum concentrations. Levetiracetam pharmacokinetics was not influenced by these anti-epileptic medicinal products.

In paediatric patients receiving up to 60 mg/kg/day, there has been no clear evidence of clinically significant drug interactions, which is consistent with formal pharmacokinetic studies in adults.

In children to adolescents with epilepsy (4 to 17 years) a retrospective assessment of pharmacokinetic interactions confirmed that adjunctive therapy with levetiracetam did not influence the steady-state serum concentrations of concomitantly administered valproate, carbamazepine, topiramate and lamotrigine. Data suggests that levetiracetam clearance increased by 22% as a result of enzyme-inducing anti-epileptic medicinal products. Dosage adjustment is not required.

Levetiracetam pharmacokinetic studies demonstrated a lack of interaction with warfarin, oral contraceptives (levonorgestrel and ethinylestradiol) and digoxin. Prothrombin times and endocrine parameters (progesterone and LH) were not modified.

No data on the absorption of levetiracetam through the influence of antacids is available.

4.6 Fertility, Pregnancy and Lactation

Effects on Fertility

Male and female fertility or reproductive performance was not observed to be adversely affected in rats administered at least two weeks prior to and throughout mating, at oral doses up to 1800 mg/kg/day (approximately 6 times the maximum recommended human dose on a mg/m^2). There is no human data on the effects of levetiracetam on male or female fertility.

Use in Pregnancy

Category B3

In rabbits and rats, foetal levels of levetiracetam and/or its metabolites approximate maternal plasma levels as they cross the placenta. At doses similar to or greater than human therapeutic doses in rabbits and rats, there was evidence of developmental toxicity from levetiracetam.

Oral administration to female rats from two weeks prior to mating and throughout pregnancy and lactation was associated with increased incidences of minor foetal skeletal abnormalities and retarded offspring growth pre- and/or postnatally at doses ≥350 mg/kg/day (approximately equivalent to the maximal recommended clinical dose of 3000 mg/day on a mg/m^2 basis) and with increased pup mortality and offspring behavioural alterations at a dose of 1800 mg/kg/day (6 times the maximal human dose on a mg/m^2 basis). The developmental no-effect dose was 70 mg/kg/day (equivalent to 0.2 times the maximal human dose on a mg/m^2 basis). There was no overt maternal toxicity at the doses used in this study.

Oral administration to pregnant rabbits during the period of organogenesis resulted in increased embryofoetal mortality and increased incidences of minor foetal skeletal abnormalities at doses ≥600 mg/kg/day (about 4 times the maximal human dose on a mg/m^2 basis) and in decreased foetal weights and increased incidences of minor foetal skeletal anomalies at a dose of 1800 mg/kg/day (12 times the maximal human dose on a mg/m^2 basis). The developmental no-effect dose was 200 mg/kg/day (1.3 times the maximal human dose on a mg/m^2 basis). Maternal toxicity was also observed at 1800 mg/kg/day.

Oral administration to pregnant rats during the period of organogenesis resulted in reduced foetal weight and increased incidence of embryofoetal mortality and increased incidence of foetal skeletal variations at a dose of 3600 mg/kg/day (12 times the maximal human dose on a mg/m^2 basis). The developmental no-effect dose was 1200 mg/kg/day (4 times the maximal human dose on a mg/m^2 basis). There was no overt maternal toxicity.

Oral administration to rats during the late gestation and throughout lactation produced no adverse developmental or maternal effects at doses of up to 1800 mg/kg/day (6 times the maximal human dose on a mg/m^2 basis).

In dogs and rats, in neonatal and juvenile studies, there were no adverse effects seen as demonstrated for any of the standard developmental or maturation endpoints at doses corresponding to 30 times the maximum recommended human dose, ie. up to 1800 mg/kg/day.

As a result of anti-epileptic medication, the risk of having an abnormal child is far outweighed by the dangers to the foetus and mother of uncontrolled epilepsy.

It is recommended that:

- pre-pregnancy counselling is provided to women on AEDs with regard to the risk of foetal abnormalities;
- during pregnancy, AEDs should be continued and as the risk of abnormality is greater in women taking combined medication, monotherapy should be used if possible at the lowest effective dose;
- at least four weeks prior to conception and continuing for twelve weeks after conception, folic acid supplementation (5 mg) should be taken;
- for the pregnant patient taking AEDs, specialist prenatal diagnosis together with detailed mid-trimester ultrasound should be undertaken and offered.

A significant amount of post-marketing reports (more than 1,200 outcomes for polytherapy and 1,800 outcomes for exposed monotherapy) do not suggest an increased risk of major malformations or additional adverse outcomes in pregnant women who had epilepsy and were on levetiracetam therapy.

In most cases, treatment with numerous anti-epileptic medicines (including polytherapy with levetiracetam) in comparison to monotherapy is linked with a greater risk of major malformations.

Only if the potential benefit justifies the potential risk to the foetus should levetiracetam be used during pregnancy. Physiological changes during pregnancy may affect levetiracetam concentration, as with other AEDs. Reports of decreased levetiracetam concentrations have been reported during pregnancy. This decrease is more pronounced during the third trimester (up to 60% of baseline concentration before pregnancy).

Use in Lactation

In lactating rats, levetiracetam and/or its metabolites are excreted in milk. Three hours after oral administration, peak milk concentrations occur (milk/plasma ratio of 0.9).

In human breast milk, levetiracetam is excreted. A decision should be made whether to discontinue breastfeeding or discontinue levetiracetam because of the potential for serious adverse reactions in breastfeeding infants. Such a decision should take into account the importance of levetiracetam to the mother.

4.7 Effects on Ability to Drive and Use Machines

No studies have been completed to evaluate the effects of levetiracetam on the ability of levetiracetam patients to drive and use machines. Some patients, due to different patient sensitivity, might experience somnolence or other CNS related symptoms at the beginning of treatment or following a dosage increase. In those patients, caution is recommended when performing skilled tasks, eg. driving vehicles, or operating machinery.

4.8 Undesirable Effects

The prescriber should be aware that the adverse event incidence figures in the following tables were obtained when levetiracetam was added to concurrent anti-epileptic therapy. It is not possible in all cases to determine which agent/s, if any, were responsible for the adverse effects. The following tables identify adverse experiences during clinical studies. Patient characteristics and other factors may differ in the course of usual medical practice and therefore the following studies make it difficult to predict the frequency of adverse experiences.

Adult Patients

Levetiracetam has been administered to more than 3,000 subjects and patients. 185 for >3 years, 366 for >2 years, 592 for >1 year and 780 patients were treated for >6 months.

In controlled clinical trials, in a total of 1,023 adult patients with epilepsy, levetiracetam was used to treat 672 patients and 351 were given placebo.

Serious drug-related treatment-emergent adverse events were experienced by patients in placebo-controlled trials. Patients in the levetiracetam group that experienced serious drug-related treatment-emergent adverse events accounted for 2.4% and in the placebo group this was 2.0%. In placebo-

controlled studies, 46.4% of levetiracetam patients experienced drug-related treatment-emergent adverse events and 42.2% of placebo patients.

Very Common Adverse Events (>10%)

The very common adverse events (>10%) were accidental injury, asthenia, infection, headache and somnolence. Accidental injury was more common in the placebo group while asthenia, infection and somnolence appeared to occur more frequently in levetiracetam treated patients, and headache was similarly reported in the two groups.

Table 4: Incidence percentages of very common treatment-emergent adverse events in placebo-controlled studies in adults – as defined by body system

Body System/Adverse Event	Number of Placebo Patients = 351 Percentage (%)	Number of Patients Treated With Levetiracetam = 672 Percentage (%)
Nervous System		
Somnolence	9.7	14.9
Whole Body		
Accidental injury	16.5	10.3
Headache	13.7	13.1
Asthenia	9.7	14.1
Infection	7.4	13.2

Incidence and severity of CNS related adverse effects in the pooled safety analysis decrease over time, although there was no clear dose-response relationship.

The term “infection” includes symptoms of community acquired infections (common cold and upper respiratory tract infections), more than 93% of the events are categorised under the COSTART preferred term “infection”. The other infections (urinary tract infections, lower respiratory tract infections, etc) had no increase in incidence.

Although small, statistically significant decreases were seen in mean hemoglobin (0.9 g/L), mean hematocrit (0.38%) and in total mean RBC count (0.03 x $10^6/mm^2$) in levetiracetam-treated patients compared to those given the placebo.

A total of 2.4% of treated and 1.4% of placebo patients had at least one possibly significant (≤1.0 x 10^9/L) decreased neutrophil count and 3.2% of treated and 1.8% of placebo patients had at least one possibly significant (≤2.8 x 10^9/L) decreased WBC count. With the continuation of treatment, all but one of the treated patients with a low neutrophil count rose towards or to baseline treatment. The low neutrophil counts were not a cause for discontinuation of treatment for any patients.

Common Adverse Events (>1%, <10%)

Table 5: Common treatment-emergent adverse events percentage incidence in placebo-controlled studies

Body System/Adverse Event	Number of Placebo Patients = 351 Percentage (%)	Number of Patients Treated With Levetiracetam = 672 Percentage (%)
Nervous System		

Body System/Adverse Event	Number of Placebo Patients = 351 Percentage (%)	Number of Patients Treated With Levetiracetam = 672 Percentage (%)
Amnesia	0.3	1.6
Anxiety	1.1	1.6
Ataxia	1.4	2.5
Convulsion	6.8	6.0
Depression	2.3	4.0
Dizziness	4.3	9.2
Emotional lability	0.3	1.6
Insomnia	2.8	3.0
Nervousness	1.7	3.9
Paraesthesia	1.7	1.9
Abnormal thinking	1.4	1.5
Tremor	1.7	1.5
Vertigo	1.4	2.5
Digestive System		
Anorexia	2.0	2.4
Diarrhoea	5.1	4.2
Dyspepsia	3.4	2.8
Gastroenteritis	0.9	1.2
Gingivitis	0.6	1.2
Nausea	4.6	4.2
Tooth disorder	0.6	1.5
Vomiting	2.0	2.2
Whole Body		
Abdominal pain	5.1	3.7
Back pain	4.6	4.0
Chest pain	1.1	1.3
Drug level increased	0.9	1.3
Fever	1.7	1.3
Flu syndrome	6.0	4.2
Hostility	0.6	2.1
Pain	6.6	6.5
Nutritional/Metabolic Disorders		
Weight gain	1.1	1.2
Lymph and Haemic System		
Ecchymosis	1.1	1.5
Skin and Appendages		
Rash	4.0	2.8
Urogenital System		
Urinary tract infection	3.4	1.9
Special Senses		
Amblyopia	1.4	1.2
Diplopia	1.7	2.4
Otitis media	0.9	1.2
Respiratory System		
Bronchitis	1.4	1.3
Cough increased	1.7	2.1

Body System/Adverse Event	Number of Placebo Patients = 351 Percentage (%)	Number of Patients Treated With Levetiracetam = 672 Percentage (%)
Pharyngitis	3.7	5.7
Rhinitis	2.6	4.3
Sinusitis	0.9	2.1

The incidence of serious adverse events in placebo controlled studies was 8.9% in the placebo group compared to 9.9% in the levetiracetam group. For a population of patients with epilepsy many of these adverse events are typical. The serious adverse events which occurred in more than 1% of patients were accidental injury (1.6% in both levetiracetam and placebo group) and convulsion (1.8% in levetiracetam group compared to 1.4% in placebo group).

Paediatric Patients

A paediatric patient study (4 to 16 years of age) showed that 40.2% in the placebo group and 55.4% of the levetiracetam paediatric patients experienced undesirable effects. With paediatric patients that experienced serious undesirable effects, 1.0% were taking placebo and 0.0% were taking levetiracetam. 20.6% of patients receiving placebo and 16.8% receiving levetiracetam, in the paediatric clinical study, either discontinued or had a dose reduction as a result of an adverse event. In the paediatric population, the most commonly reported undesirable effects were hostility, somnolence, emotional lability, nervousness, anorexia, agitation, headache and asthenia. In paediatric patients, safety results were consistent with the safety profile of levetiracetam in adults, except for psychiatric and behavioural undesirable effects which were less common in adults than in children (18.6% in adults compared to 38.6% in children). There was also a lower incidence of behavioural psychiatric adverse events in the adult placebo group (10.5%) compared to the children placebo group (27.8%) which confirmed that the relative risk was similar in children to adults.

Table 6: Treatment-emergent adverse events percentage incidence (adverse events that occurred in at least 2% of levetiracetam-treated patients and occurred more frequently than placebo-treated patients) in a placebo-controlled, add-on study in paediatric patients aged 4-16 years, by body system

Body System/Adverse Event	Number of Placebo Patients = 97 Percentage (%)	Number of Patients Treated With Levetiracetam = 101 Percentage (%)
Nervous System		
Somnolence	11	23
Hostility	6	12
Nervousness	2	10
Personality disorder	7	8
Dizziness	2	7
Emotional lability	4	6
Agitation	1	6
Depression	1	3
Vertigo	1	3
Reflexes increased	1	2
Confusion	0	2
Lymph and Haemic System		
Ecchymosis	1	4
Whole Body		
Accidental injury	10	17

Asthenia	3	9
Pain	3	6
Flu syndrome	2	3
Face oedema	1	2
Neck pain	1	2
Viral infection	1	2
Digestive System		
Vomiting	13	15
Anorexia	8	13
Diarrhoea	7	8
Gastroenteritis	2	4
Constipation	1	3
Urogenital System		
Albuminuria	0	4
Urine abnormality	1	2
Special Senses		
Conjunctivitis	2	3
Amblyopia	0	2
Ear pain	0	2
Appendages and Skin		
Pruritis	0	2
Skin discolouration	0	2
Vesiculobullous rash	0	2
Respiratory System		
Rhinitis	8	13
Cough increased	7	11
Pharyngitis	8	10
Asthma	1	2
Metabolic/Nutritional Disorders		
Dehydration	1	2

In paediatric patients on placebo versus levetiracetam, the following adverse effects occurred in 2% or more of paediatric patients and were more frequent in placebo patients: sinusitis, abdominal pain, status epilepticus (not otherwise specified), allergic reaction, convulsion, ataxia, epistaxis, fever, headache, hyperkinesia, infection, insomnia, nausea, otitis media, tremor, rash, abnormal thinking, and urinary incontinence.

Other Controlled Clinical Trials

In additional controlled clinical trials, the following adverse effects, listed by body system, have been observed.

General Disorders
Very Common: fatigue.

Lymphatic and Blood System Disorders
Common: thrombocytopenia.

Eye Disorders
Common: vision blurred.

Respiratory System
Common: nasopharyngitis.

Nervous System
Common: memory impairment, disturbance in attention balance-disorder.

Connective Tissue and Musculoskeletal Disorders
Common: myalgia.

Psychiatric Disorders
Common: personality disorder, irritability, mood swings.

Skin and Subcutaneous Tissue Disorders
Common: pruritis, eczema.

Post-marketing Experience

Psychiatric and nervous system disorders have been most frequently reported in post-marketing experience. Additional to the adverse effects mentioned and listed above, the following have been reported during clinical studies post-marketing. There is insufficient data to determine an incidence estimate in the population to be treated.

Psychiatric Disorders
Aggression, abnormal behaviour, confusion, anger, hallucination, suicide, psychotic disorder, suicidal ideation, panic attack, delirium and attempted suicide.

Blood and Lymphatic System Disorders
Neutropenia, pancytopenia with bone marrow suppression identified in some cases, and agranulocytosis, leucopenia.

Biliary and Liver Disorders
Abnormal liver function test, hepatitis, and hepatic failure.

Nutritional and Metabolic Disorders
Pancreatitis, hyponatraemia, weight loss.

Subcutaneous and Skin Disorders
Erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, alopecia (in several alopecia cases upon levetiracetam being discontinued, recovery was observed).

Nervous System Disorders
Choreoathetosis, dyskinesia, gait disturbance and lethargy.

Immune System Disorders
Drug reaction with eosinophilia and systemic symptoms (DRESS) and anaphylaxis.

Musculoskeletal and Connective Tissue Disorders
Increase of blood creatinine phosphokinase, muscular weakness and rhabdomyolysis.

Renal and Urinary Disorders
Acute kidney injury.

Reports of Selected Adverse Reactions

In Japanese patients, the prevalence of rhabdomyolysis and an increase in blood creatinine phosphokinase is significantly greater in comparison to patients who are not Japanese.

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

In the clinical development program, the highest known dose of levetiracetam received was 6000 mg/day. There were no adverse events in the few known cases of overdose in clinical trials except for drowsiness.

In post-marketing cases of levetiracetam overdose, the following adverse events were observed: agitation, aggression, coma, depressed level of consciousness, somnolence and respiratory depression.

Levetiracetam has no specific antidote for overdose. The stomach may be emptied by gastric lavage or by induction of emesis after an acute overdose. Symptomatic treatment will be required for an overdose and may include haemodialysis.

The levetiracetam dialyser extraction efficiency is 60% and for the major metabolite (ucb L057) dialyser extraction efficiency is 74%.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: anti-epileptics, other anti-epileptics, ATC code: N03AX14.

Mechanism of Action

While the exact mechanism of action by which levetiracetam causes seizure protection still needs to be fully determined, this mechanism of action differs from the existing AEDs. Levetiracetam does not appear to alter basic cell characteristics and normal neurotransmission during *in vitro* and *in vivo* experiments. No interactions with traditional drug-targets involved in inhibitory and excitatory neuro-transmission have been observed. The mechanism of action may relate to an interaction with a specific and stereo-selective binding site that is only found within the central nervous system.

Levetiracetam *in vitro* studies, report the reduction in the release of Ca^{2+} from intraneuronal stores and the effect on intraneuronal Ca^{2+} levels by partial inhibition of N-type Ca^{2+} currents. Levetiracetam in addition reverses the reduction in: GABA-; and glycine gated currents induced by β-carbolines and zinc. *In vitro* studies for levetiracetam have shown binding to a specific site in the brain tissue of rodents. This specific site is believed to be involved in vesicle fusion and neurotransmitter exocytosis and is known as the synaptic vesicle protein 2A (SV2A). In audiogenic seizure-prone mice, a rank order of affinity was

shown for SV2A by levetiracetam and related analogues, which correlated with the potency of their antiseizure activity. Levetiracetam's anti-epileptic mechanism of action may be due to interaction with SV2A.

Pharmacodynamic Effects

In Animals

In the classical screening models of anticonvulsants, levetiracetam is not active, however levetiracetam in a broad range of animal models induces potent protection in both primary and partial generalised seizures.

By dose-dependently inhibiting the development of kindling, levetiracetam displays potential anti-epileptogenic properties. This occurs even after the discontinuation of levetiracetam.

Clinical studies in animals found that levetiracetam has an unusually high safety margin between therapeutic doses and doses inducing adverse effects. There was no decrease on the seizure threshold after withdrawal from chronic treatment. An absence of undesirable effects on cognitive function and anxiolytic action and have also been observed.

In seizure models, ucb L057, the major metabolite, is inactive.

In Humans

The broad spectrum preclinical pharmacological profile is confirmed in both generalised and partial human epilepsy models (photoparoxysmal response/epileptiform discharge).

Clinical Trials

Effectiveness in Partial Onset Seizures in Adult Patients With Epilepsy

Monotherapy

A monotherapy non-inferiority comparison study on levetiracetam and carbamazepine (controlled release) monotherapy was completed in patients who had recently been diagnosed with epilepsy who were 16 years or older in a double-blind, parallel group study. This study was completed over 13 countries in Europe and South Africa and over 85 centres. The epileptic seizures were all classified in accordance to the International Classification of Epileptic Seizures which were either type IA (unprovoked partial seizures – simple partial seizures with consciousness that was unaffected), type IB (complex partial seizures with consciousness that was impaired), type IC (secondary generalised partial seizures (with a clear focal origin)), or type IIE (a generalised tonic-clonic seizure (with an unknown clear focal origin)).

Following a 1-week period of screening, subjects that were eligible were stratified by the type of seizure (type IA/IB/IC or type IC/IIE clear focal origin unknown) and randomly allocated to be administered carbamazepine (controlled release) or levetiracetam (N=291 and N=285, respectively), over a duration of up to 121 weeks conditional on their response to treatment.

A controlled release formula of carbamazepine was conservatively used to decrease any unwanted adverse effects. The maximum duration for a patient was 121 weeks.

Following the 1 week period of screening (no medicine intake), the patient entered a randomised 2 week up-titration period to obtain the first daily dose target of 1000 mg for levetiracetam and 400 mg for

carbamazepine. This was followed by a 1 week period of stabilisation and a period of evaluation over 26 weeks to achieve the primary efficacy endpoint of 6 month seizure freedom. This was then followed by a further 26 weeks of a period of maintenance to evaluate safety and efficacy.

In the event of a seizure occurring in the period of evaluation, the dose was increased over a period of 2 weeks to the second daily dose target of 2000 mg for levetiracetam and 800 mg for carbamazepine. A period of stabilisation of 1 week followed with a new period of evaluation over 26 weeks and a period of maintenance for a further 26 weeks. In the event of a seizure occurring in the period of evaluation at the second target dose level, the same was true where the dose was increased over a period of 2 weeks to the third daily dose target of 3000 mg for levetiracetam and 1200 mg for carbamazepine. A period of stabilisation of 1-week followed with a new period of evaluation over 26 weeks and a period of maintenance of a further 26 weeks. Alternative option: in the event that a subject did not respond well to the second or third drug dose target, the patient had an opportunity, throughout the period of evaluation or maintenance, to have one decrease of dosage to an intermediate dose, where levetiracetam was decreased by 500 mg per day and carbamazepine was decreased by 200 mg per day. The study would then continue on this basis. The individual could not continue the previous dosage and could not have any additional up-titration in the event of an occurrence of a new seizure.

A total of 576 individuals were randomised. Approximately half of the individuals finished the study in each treatment group (54.0% for levetiracetam randomised patients and 53.6% for carbamazepine randomised patients). The type of seizure categories distribution was comparable in both the levetiracetam and carbamazepine groups, with approximately 86.7% of patients classified as having partial seizures with a clear focus origin. Most patients stayed at the level 1 dose (81.7% and 73.4% for subjects randomised to carbamazepine and levetiracetam, respectively).

The primary endpoint prospectively outlined was the number of patients from the PP population with freedom of seizures over 6 months at the final evaluated dose.

73% (173 patients) of the PP subjects in the levetiracetam treatment arm were free of seizures for 6 months or more at the final evaluated dose, in comparison to 72.8% (171 patients) in the carbamazepine treatment arm. In a logistic regression model, the adjusted absolute difference of levetiracetam and carbamazepine (95% 2 sided CI) incorporated a factor for the type of seizure category as previously evaluated (type IA/IB/IC vs type IC/IIE) totalled 0.2% (-7.8%; 8.2%, respectively). The confidence interval lower limit of -7.8% was over the non-inferiority limit fixed by the protocol of -15% for this analysis of primary efficacy. Therefore, levetiracetam can be regarded as non-inferior to carbamazepine on the amount of patients that were free of seizures more than 6 months at the first dose evaluated in the population. In consideration of the additional clinically relevant end point, 56.6% of levetiracetam patients and 58.5% of carbamazepine patients were free of seizures for one year.

Add-on Therapy

The effectiveness of levetiracetam as adjunctive therapy (added to other AEDs) in adults was established in three multicentre, randomised, double-blind, placebo-controlled clinical studies in patients who had refractory partial onset seizures with or without secondary generalisation. In these studies, 904 patients were randomised to placebo, 1000 mg, 2000 mg or 3000 mg/day.

Patients enrolled in Study 1 or Study 2 had refractory partial onset seizures for at least 2 years and had taken two or more classical AEDs. Patients enrolled in Study 3 had refractory partial onset seizures for at least 1 year and had taken one classical AED. At the time of the study, patients were taking a stable dose regimen of at least one and could take a maximum of two AEDs. During the baseline period, patients had to have experienced at least two partial onset seizures during each 4-week period.

Study 1

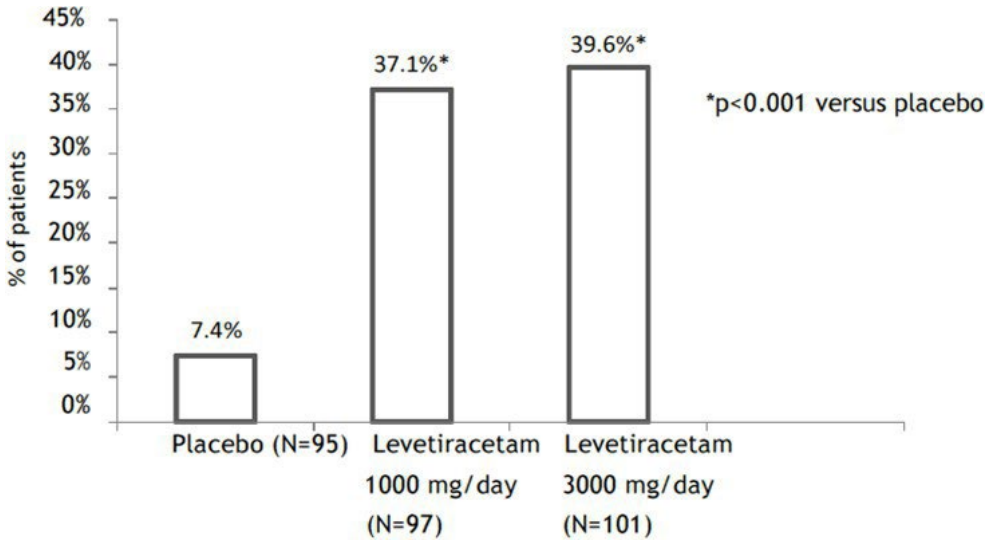
Study 1 was a double-blind, placebo-controlled, parallel-group study conducted at 41 sites in the United States comparing levetiracetam 1000 mg/day (N=97), levetiracetam 3000 mg/day (N=101) and placebo (N=95) given in equally divided doses twice daily. After a prospective baseline period of 12 weeks, patients were randomised to one of the three treatment groups described above. The 18-week treatment period consisted of a 6-week titration period, followed by a 12-week fixed dose evaluation period, during which concomitant AED regimens were held constant. The primary measure of effectiveness was a between group comparison of the percent reduction in weekly partial seizure frequency relative to placebo over the entire randomised treatment period (titration + evaluation period). Secondary outcome variables included the responder rate (incidence of patients with ≥50% reduction from baseline in partial onset seizure frequency). The results of the analysis of Study 1 are displayed in **Table 7**.

Table 7: Reduction in mean over placebo in weekly frequency of partial onset seizures in Study 1

	Placebo (N=95)	**Levetiracetam 1000 mg/day (N=97)**	**Levetiracetam 3000 mg/day (N=101)**
Percent reduction in partial seizure frequency over placebo	-	26.1% p <0.001	30.1% p <0.001

The percentage of patients (y-axis) who achieved ≥50% reduction in weekly seizure rates from baseline in partial onset seizure frequency over the entire randomised treatment period (titration + evaluation period) within the three treatment groups (x-axis) is presented in **Figure 1**.

Figure 1: Responder rate (≥50% reduction from baseline) in Study 1



Study 2

Study 2 was a double-blind, placebo-controlled, crossover study conducted at 62 centres in Europe comparing levetiracetam 1000 mg/day (N=106), levetiracetam 2000 mg/day (N=105) and placebo (N=111) given in equally divided doses twice daily.

The first period of the study (Period A) was designed to be analysed as a parallel-group study. After a prospective baseline period of up to 12 weeks, patients were randomised to one of the three treatment groups described above. The 16-week treatment period consisted of the 4-week titration period

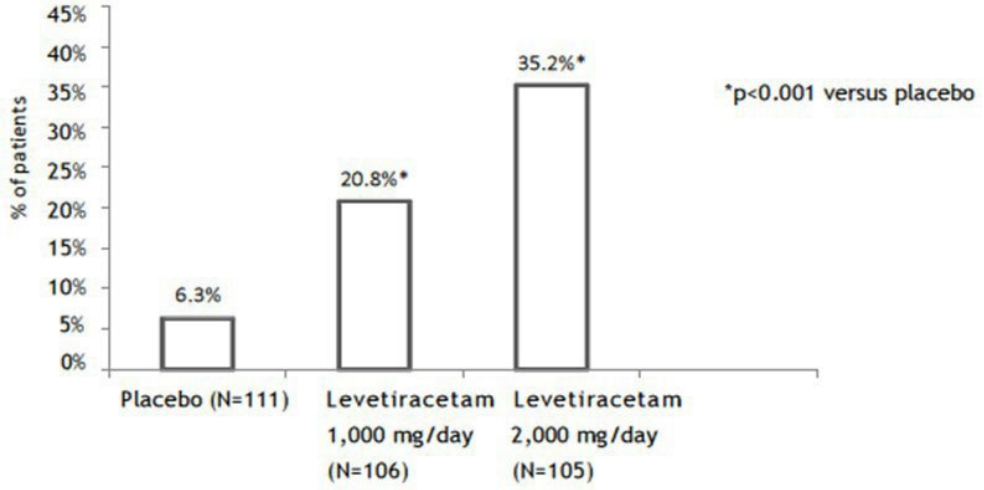
followed by a 12-week fixed dose evaluation period, during which concomitant AED regimens were held constant. The primary measure of effectiveness was a between group comparison of the percent reduction in weekly partial seizure frequency relative to placebo over the entire randomised treatment period (titration + evaluation period). Secondary outcome variables included the responder rate (incidence of patients with ≥50% reduction from baseline in partial onset seizure frequency). The results of the analysis of Period A are displayed in **Table 8**.

Table 8: Reduction in mean over placebo in weekly frequency of partial onset seizures in Study 2 – Period A

	Placebo (N=111)	**Levetiracetam 1000 mg/day (N=106)**	**Levetiracetam 3000 mg/day (N=105)**
Percent reduction in partial seizure frequency over placebo	-	17.1% p ≤0.001	21.4% p ≤0.001

The percentage of patients (y-axis) who achieved ≥ 50% reduction in weekly seizure rates from baseline in partial onset seizure frequency over the entire randomised treatment period (titration + evaluation period) within the three treatment groups (x-axis) is presented in Figure 2.

Figure 2: Responder rate (≥50% reduction from baseline) in Study 2 – Period A



The comparison of levetiracetam 2000 mg/day to levetiracetam 1000 mg/day for responder rate was statistically significant (P=0.02). Analysis of the trial as a crossover yielded similar results.

Study 3

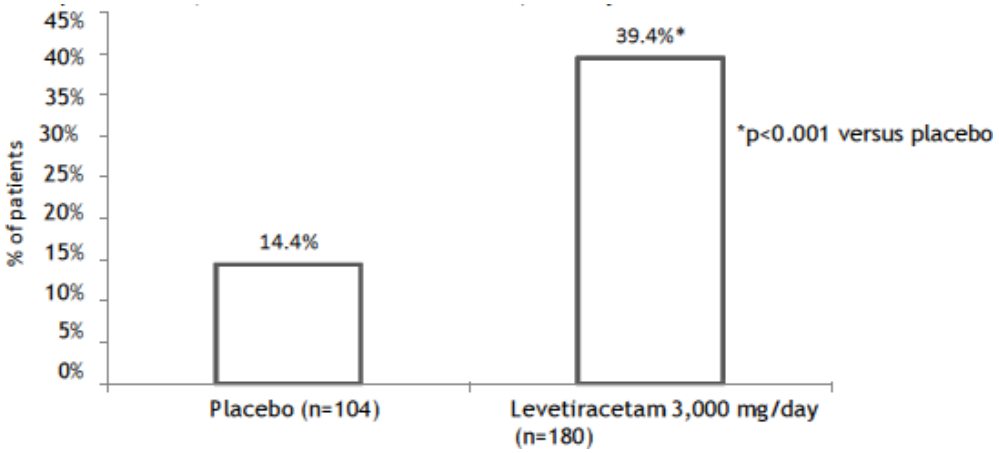
Study 3 was a double-blind, placebo-controlled, parallel-group study conducted at 47 centres in Europe comparing levetiracetam 3000 mg/day (N=180) and placebo (N=104) in patients with refractory partial onset seizures, with or without secondary generalisation, receiving only one concomitant AED. Study drug was given in two divided doses. After a prospective baseline period of 12 weeks, patients were randomised to one of two treatment groups described above. The 16-week treatment period consisted of a 4-week titration period, followed by a 12-week fixed dose evaluation period, during which concomitant AED doses were held constant. The primary measure of effectiveness was a between group comparison of the percent reduction in weekly seizure frequency relative to placebo over the entire randomised treatment period (titration + evaluation period). Secondary outcome variables included the responder rate (incidence of patients with ≥50% reduction from baseline in partial onset seizure frequency). **Table 9** displays the results of the analysis of Study 3.

Table 9: Reduction in mean over placebo in weekly frequency of partial onset seizures in Study 3

	Placebo (N=104)	Levetiracetam 3000 mg/day (N=180)
Percent reduction in partial seizure frequency over placebo	-	23.0% p ≤0.001

The percentage of patients (y-axis) who achieved ≥50% reduction in weekly seizure rates from baseline in partial onset seizure frequency over the entire randomised treatment period (titration + evaluation period) within the two treatment groups (x-axis) is presented in **Figure 3**.

Figure 3: Responder rate (≥50% reduction from baseline) in Study 3



Effectiveness in Partial Onset Seizures in Paediatric Patients with Epilepsy

The effectiveness of levetiracetam as adjunctive therapy (added to other AEDs) in paediatric patients was established in a multicentre, randomised double-blind, placebo-controlled study, conducted at 60 sites in North America, in children 4 to 16 years of age with partial seizures uncontrolled by standard AEDs. Eligible patients on a steady dose of 1-2 AEDs, who still experienced at least 4 partial onset seizures during the 4 weeks prior to screening, as well as at least 4 partial onset seizures in each of the two 4-week baseline periods, were randomised to receive either levetiracetam or placebo. The population included 198 patients (levetiracetam N=101, placebo N=97) with uncontrolled partial onset seizures, whether or not secondarily generalised. The study consisted of an 8-week baseline period and 4-week titration period followed by a 10-week evaluation period. Dosing was initiated at a target dose of 20 mg/kg/day in two divided doses. During the treatment period, levetiracetam doses were adjusted in 20 mg/kg/day increments, at 2-week intervals to the target dose of 60 mg/kg/day (or 40 mg/kg/day as a maximum tolerated dose).

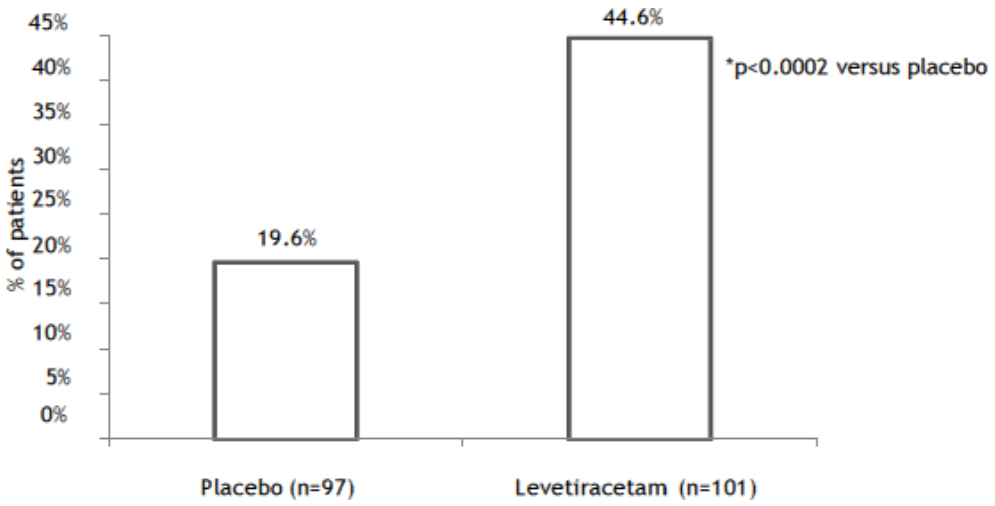
The primary measure of effectiveness was a between group comparison of the percent reduction in weekly partial seizure frequency relative to placebo over the entire 14-week randomised treatment period (titration + evaluation period). Secondary outcome variables included the responder rate (incidence of patients with ≥ 50% reduction from baseline in partial onset seizure frequency per week). **Table 10** displays the results of this study.

Table 10: Reduction in mean over placebo in weekly frequency of partial onset seizures

	Placebo (N=97)	Levetiracetam (N=101)
Percent reduction in partial seizure frequency over placebo	-	26.8% p=0.0002

The percentage of patients (y-axis) who achieved ≥50% reduction in weekly seizure rates from baseline in partial onset seizure frequency over the entire randomised treatment period (titration + evaluation period) within the two treatment groups (x-axis) is presented in **Figure 4**.

Figure 4: Responder rate (≥50% reduction from baseline)



Effectiveness in Myoclonic Seizures in Patients >12 Years of Age With Juvenile Myoclonic Epilepsy (JME)

The effectiveness of levetiracetam as adjunctive therapy in patients 12 years of age and older with JME experiencing myoclonic seizures was established in one multicentre, randomised, double-blind, placebo-controlled study, conducted at 37 sites in 14 countries. Eligible patients on a stable dose of 1 AED experiencing one or more myoclonic seizures per day for at least 8 days during the prospective 8-week baseline period were randomised to either levetiracetam or placebo. The population included 120 patients (levetiracetam N=60, placebo N=60) with IGE which included juvenile myoclonic epilepsy, juvenile absence epilepsy, or epilepsy with generalised tonic-clonic seizures on awakening. The majority were patients with juvenile myoclonic epilepsy. Patients were titrated over 4 weeks to a target dose of 3000 mg/day and treated at a stable dose of 3000 mg/day over 12 weeks (evaluation period). Study drug was given in 2 divided doses.

The primary measure of effectiveness was the proportion of patients with at least 50% reduction in the number of days per week with one or more myoclonic seizures during the treatment period (titration + evaluation periods) as compared to baseline. Secondary outcome variables included seizure frequency per week over the treatment period. **Table 11** displays the results of this study.

Table 11: Responder rate (>50% reduction from baseline) in myoclonic seizure days per week for patients with JME

	Placebo (N=60)	Levetiracetam (N=60)
Percentage of responders	23.3%	58.3% p=0.0002

Effectiveness in Primary Generalised Tonic-clonic Seizures in Patients >4 Years of Age With Idiopathic Generalised Epilepsy

The effectiveness of levetiracetam as adjunctive therapy (added to other AEDs) in patients 4 years of age and older with IGE experiencing PGTC seizures was established in one multicentre, randomised, double-blind, placebo-controlled study, conducted at 50 sites in 8 countries. Eligible patients on a stable dose of 1 or 2 AEDs experiencing at least 3 PGTC seizures during the 8-week combined baseline period (at least 1 PGTC seizure during the 4 weeks prior to the prospective baseline period and at least 1 PGTC seizure during the 4-week prospective baseline period) were randomised to either levetiracetam or placebo. The 8-week combined baseline period is referred to as “baseline” in the remainder of this section. The population included 164 patients (levetiracetam N=80, placebo N=84) with IGE (predominately juvenile myoclonic epilepsy, juvenile absence epilepsy, childhood absence epilepsy, or epilepsy with Grand Mal seizures on awakening) experiencing PGTC seizures. Each of these syndromes of IGE was well represented in this patient population. Patients were titrated over 4 weeks to a target dose of 3000 mg/day for adults or a paediatric target dose of 60 mg/kg/day and treated at a stable dose of 3000 mg/day (or 60 mg/kg/day for children) over 20 weeks (evaluation period). Study drug was given in 2 equally divided doses per day.

The primary measure of effectiveness was the percent reduction from baseline in weekly PGTC seizure frequency for levetiracetam and placebo treatment groups over the treatment period (titration + evaluation periods). There was a statistically significant decrease from baseline in PGTC frequency in the levetiracetam-treated patients compared to the placebo-treated patients. **Table 12** displays the results of this study.

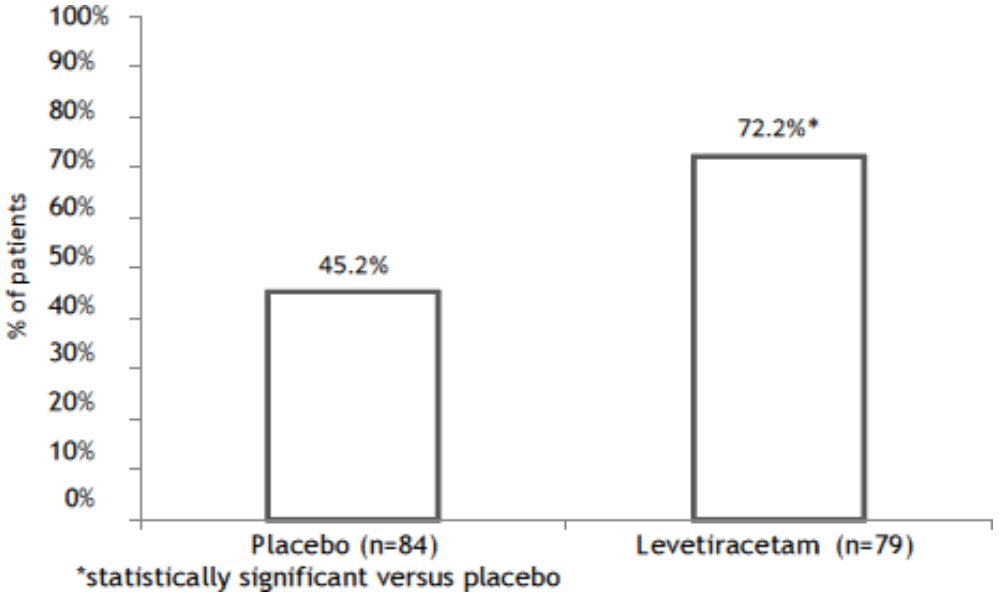
Table 12: Median percent reduction from baseline in PGTC seizure frequency per week

	Placebo (N=84)	Levetiracetam (N=78)
Percent reduction in PGTC seizure frequency	44.6%	77.6%*

* Statistically significant versus placebo.

The percentage of patients (y-axis) who achieved >50% reduction in weekly seizure rates from baseline in PGTC seizure frequency over the entire randomised treatment period (titration + evaluation period) within the two treatment groups (x-axis) is presented in **Figure 5**.

Figure 5: Responder rate (≥50% reduction from baseline) in PGTC seizure frequency per week



When levetiracetam was used to treat PGTC seizures in adults and adolescents with IGE, there was no effect on the frequency of absences.

5.2 Pharmacokinetic Properties

Levetiracetam is a permeable and highly soluble compound with a linear pharmacokinetic profile and low inter-subject and intra-subject variability. After repeated administration there is no modification of clearance.

Levetiracetam 1500 mg given twice daily by IV infusion for 4 days confirms this pharmacokinetic profile.

In both adults and children there is a significant correlation between saliva and plasma levetiracetam concentrations. The ratio of saliva to plasma concentrations is 1 to 1.7 for the oral tablets and an oral solution formulation, 4 hours post dose.

Due to its complete and linear absorption, plasma levels can be predicted from the oral dose of levetiracetam expressed as mg/kg bodyweight. Therefore, there is no need for plasma level monitoring of levetiracetam.

Race, gender or circadian differences do not affect pharmacokinetics. In adult patients, the pharmacokinetic profile is comparable between epileptic patients and healthy volunteers (without epilepsy).

Three levetiracetam 500 mg tablets (1500 mg total) given orally is bioequivalent to one dose of levetiracetam 1500 mg diluted in a compatible diluent of 100 mL and administered over 15 minutes via intravenous infusion.

Administrations of levetiracetam 2500 mg and 4000 mg diluted both in 0.9% sodium chloride 100 mL and administered via intravenous infusion over 5 minutes and 15 minutes, respectively, were assessed and no safety concerns were identified in the pharmacokinetic or safety profiles.

Adults and Adolescents

Absorption

After oral administration, levetiracetam is rapidly and almost completely absorbed and has an oral absolute bioavailability close to 100%. At 1.3 hours after dosing, peak plasma concentrations (C_{max}) are reached. After a twice daily administration schedule for two days, steady state is achieved. (C_{max}) peak concentrations are typically 31 microgram/mL following a single 1000 mg dose and 43 microgram/mL following repeated 1000 mg b.i.d. dosing. Absorption is dose-independent. Absorption is not altered by food, but food slightly reduces the rate of absorption.

Distribution

Human tissue distribution data is not available. Neither the major metabolite ucb L057 or levetiracetam are significantly bound to plasma proteins (<10%). The volume of distribution of levetiracetam is close to the volume of distribution of intracellular and extracellular water which is approximately 0.5 L/kg to 0.7 L/kg.

Metabolism

The major metabolite produced from levetiracetam is ucb L057 which results from an enzymatic hydrolysis of the acetamide group. This metabolic pathway for ucb L057 accounts for 24% of the dose. Acetamide group hydrolysis was measurable in a large number of tissues including whole blood, but not plasma. Production of ucb L057, the major metabolite is not supported by liver cytochrome P450 isoforms.

Ucb L057, the major metabolite, is pharmacologically inactive.

Two minor metabolites were identified as the product of hydroxylation of the 2-oxo-pyrrolidine ring (1.6% of dose) and opening of the 2-oxo-pyrrolidine ring in position 5 (0.9% of dose). There is no *in vivo* enantiomeric interconversion of levetiracetam or its major metabolite.

Only 0.6% of the dose accounted for other unidentified components.

Levetiracetam and its primary metabolite ucb L057, *in vitro*, do not inhibit the major human liver cytochrome P450 isoforms (CYP3A4, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP1A2), expoxide hydrolysis and glucuronyl transferase (UGT1A1 and UGT1A6) activities. Valproic acid is not affected by *in vitro* glucuronidation by levetiracetam.

In a culture of human hepatocytes, levetiracetam had little effect on CYP1A1 and CYP1A2 or ethinylestradiol conjugation. There was mild induction of CYP3A4 and CYP2B6 by levetiracetam at high concentrations (680 microgram/mL), although at concentrations approximating C_{max} after repeated 1500 mg twice daily dosage, the effects were not considered biologically relevant. Therefore, the interaction of levetiracetam with other substances, or other substances interacting with levetiracetam, was considered unlikely.

Excretion

In adults, the plasma half-life was 7 ± 1 hours. The plasma half-life did not vary with route of administration, repeated administration or dose. 0.96 mL/min/kg was the mean total body clearance.

Excretion via urine, which was the major route of excretion, accounted for a mean of 95% of the dose. Approximately 93% of the dose was excreted within 48 hours. Faecal excretion accounted for only 0.3%

of the dose. The cumulative urinary excretion of the major metabolite ucb L057 was 24%, while levetiracetam accounted for 66% during the first 48 hours.

The renal clearance is 0.6 mL/min/kg, which indicates that levetiracetam excretion is via glomerular filtration, with subsequent tubular reabsorption.

The major metabolite ucb L057 is excreted by active tubular secretion, in addition to glomerular filtration, and the renal clearance is 4.2 mL/min/kg.

Elderly

The half-life is increased by 40% (10 to 11 hours) in elderly patients. This is attributed to the decrease in renal function in this patient population (see **Section 4.2 Dose and Method of Administration**).

Children (4 to 12 years of age)

In epileptic children (6 to 12 years of age) after a single dose of 20 mg/kg, the half-life of levetiracetam was 6.0 ± 1.1 hours. In epileptic children (6 to 12 years of age) the apparent body clearance was approximately 30% higher than in epileptic adults.

In epileptic children (4 to 12 years of age), levetiracetam was rapidly absorbed following repeated administration of 20 mg to 60 mg/kg/day. Half an hour to one hour after dosing, peak plasma concentrations (C_{max}) were observed. Peak plasma concentrations and area under the curve were linear and dose proportional. The apparent body clearance was 1.1 mL/min/kg and the elimination half-life was approximately 5 hours.

Infants and Children (1 month to 4 years of age)

In epileptic children (1 month to 4 years of age) after a single dose of a 10% oral solution (20 mg/kg) approximately 1 hour after dosing, peak plasma concentrations were observed and levetiracetam was rapidly absorbed. The pharmacokinetic half-life was shorter for children (5.3 hours) versus adults (7.2 hours) and the apparent clearance in children was faster (1.5 mL/min/kg) versus adults (0.96 mL/min/kg).

Renal Impairment

Levetiracetam and its major metabolite ucb L057 apparent body clearances are correlated to the creatinine clearance. The levetiracetam daily maintenance dose should be adjusted based on creatinine clearance in patients with moderate and severe renal impairment (see **Section 4.2 Dose and Method of Administration**).

In adult patients with anuric end stage renal disease, the half-life was approximately 25 hours during inter-dialytic periods and 3.1 hours during intra-dialytic periods respectively. During a typical 4 hour dialysis session, the fractional removal of levetiracetam was 51%.

Hepatic Impairment

In subjects with mild and moderate hepatic impairment, the clearance of levetiracetam was not changed. In most subjects with severe hepatic impairment, clearance was reduced by more than 50% compared to normal subjects, due to concomitant renal impairment (see **Section 4.2 Dose and Method of Administration**).

5.3 Preclinical Safety Data

Genotoxicity

Levetiracetam was negative in gene mutation assays (bacterial, Chinese hamster ovary/ HGPRT locus) and in assays for chromosomal damage *in vitro* and *in vivo* (Chinese hamster ovary cells, mouse micronucleus assay). The hydrolysis product and major human metabolite (ucb L057) was not mutagenic in bacterial reverse mutation assays or the *in vitro* mouse lymphoma assay.

Carcinogenicity

There was no evidence of carcinogenicity following administration of levetiracetam in the diet to rats or orally to mice for 104 weeks, associated with respective systemic exposures (plasma AUC) up to 4-fold and 8-fold that in humans at the maximal recommended clinical dose of 3000 mg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Levetiracetam Lupin film-coated tablets contain the following excipients:

- Maize starch
- Silica
- Colloidal anhydrous
- Croscarmellose sodium
- Povidone
- Purified water
- Microcrystalline cellulose
- Talc
- Magnesium stearate
- Levetiracetam Lupin 250 mg film-coated tablets also contain: Opadry blue AMB 84F80803
- Levetiracetam Lupin 500 mg film-coated tablets also contain: Opadry yellow AMB 84F82508
- Levetiracetam Lupin 750 mg film-coated tablets also contain: Opadry pink AMB 84F84674
- Levetiracetam Lupin 1000 mg film-coated tablets also contain: Opadry white AMB 84F58775

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

36 months.

6.4 Special Precautions for Storage

Store at or below 30°C.

6.5 Nature and Contents of Container

Levetiracetam Lupin film-coated tablets are available in strengths of 250 mg, 500 mg, 750 mg and 1000 mg levetiracetam.

All strengths are available in PVC/Al blister packs containing 60 tablets.

6.6 Special Precautions for Disposal

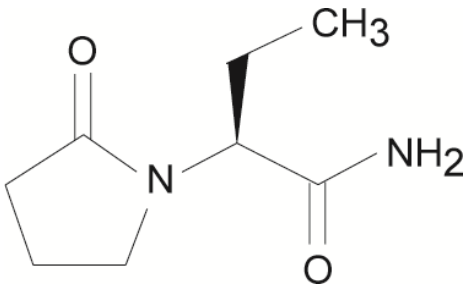
Any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical Properties

Levetiracetam is chemically unrelated to existing AEDs.

Levetiracetam is a white to off-white powder with a bitter taste and a faint odour. Levetiracetam is practically insoluble in n-hexane, sparingly soluble in acetonitrile (5.7 g/100 mL), soluble in ethanol (16.5 g/100 mL) and in methanol (53.6 g/10 mL), and freely soluble in chloroform (65.3 g/100 mL) and in water (104 g/100 mL).

Chemical Structure



Molecular Formula: $C_8H_{14}N_2O_2$
Molecular Weight: 170.21

CAS Number

102767-28-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Medicine

8 SPONSOR

Lupin NZ Limited
c/- BDO
Level 4, Building A, BDO Centre
4 Graham Street
Auckland, 1010
New Zealand

Phone: +64 9889 6972

9 DATE OF FIRST APPROVAL

4 August 2022

10 DATE OF REVISION

19 August 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of New Information
All	Trade name change to Levetiracetam Lupin
8	Change of sponsor