New Zealand Datasheet

1 PRODUCT NAME
Everet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Levetiracetam 250 mg, 500 mg, 750 mg and 1000 mg film coated tablets.
Levetiracetam 100 mg/ml oral solution.

3 PHARMACEUTICAL FORM
Everet 250 mg tablets are light blue, capsule shaped, biconvex film coated tablets, plain on both sides. Each tablet contains 250 mg levetiracetam.

Everet 500 mg tablets are yellow, capsule shaped, biconvex film coated tablets, plain on both sides. Each tablet contains 500 mg levetiracetam.

Everet 750 mg tablets are light orange, capsule shaped, biconvex film coated tablets, plain on both sides. Each tablet contains 750 mg levetiracetam.

Everet 1000 mg tablets are white, capsule shaped, biconvex film coated tablets, plain on both sides. Each tablet contains 1000 mg levetiracetam.

Everet 100 mg/ml oral solution is a clear, colourless or slightly yellowish liquid containing 100 mg/ml levetiracetam.

Do not halve tablet. Dose equivalence when the tablet is divided has not been established.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Everet tablets are indicated for:
• use in epileptic patients aged 6 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 generalized tonic-clonic seizures in adults and children from 6 years of age with idiopathic generalized epilepsy (IGE).

Everet oral solution is 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 generalized tonic-clonic seizures in adults and children from 4 years of age with idiopathic generalized epilepsy (IGE).

4.2 Dose and method of administration
Everet tablets must be taken orally, with or without food, and swallowed with liquid. The oral solution may be diluted in a glass of water. Both the film-coated tablets and oral solution may be taken with or without food. The daily dose is administered in two equal dose amounts. Do not divide the tablets.

**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 Everet may be envisaged by progressively decreasing and withdrawing the concomitant antiepileptic 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).

**Children (aged 4 to 11 years of age) and adolescents (aged 12-17 years of age) weighing less than 50kg**
The initial therapeutic dose is 10 mg/kg twice daily. Refer to 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 50kg the dosage is the same as in adults.

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

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

<table>
<thead>
<tr>
<th>Weight</th>
<th>Starting dose: 10 mg/kg twice daily</th>
<th>Maximum dose: 30 mg/kg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 kg  (1)</td>
<td>150 mg (1.5 ml) twice daily</td>
<td>450 mg (4.5 ml) twice daily</td>
</tr>
<tr>
<td>20 kg  (1)</td>
<td>200 mg (2.0 ml) twice daily</td>
<td>600 mg (6.0 ml) twice daily</td>
</tr>
<tr>
<td>25 kg</td>
<td>250 mg (2.5 ml) twice daily</td>
<td>750 mg (7.5 ml) twice daily</td>
</tr>
<tr>
<td>From 50 kg  (2)</td>
<td>500 mg (5.0 ml) twice daily</td>
<td>1500 mg (15 ml) twice daily</td>
</tr>
</tbody>
</table>

(1) Children 20 kg or less should preferably start the treatment with Everet 100 mg/ml 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 are 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)

<table>
<thead>
<tr>
<th>Group</th>
<th>Creatinine clearance (mL/min)</th>
<th>Frequency</th>
<th>Dosage (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-stage renal disease patients undergoing dialysis (A 750mg loading dose is recommended on the first day of treatment with levetiracetam).</td>
<td>-</td>
<td>Once (following dialysis, a 250 to 500mg supplemental dose is recommended).</td>
<td>500 to 1,000</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt; 30</td>
<td>Twice</td>
<td>250 to 500</td>
</tr>
<tr>
<td>Moderate</td>
<td>30-49</td>
<td>Twice</td>
<td>250 to 750</td>
</tr>
<tr>
<td>Mild</td>
<td>50-79</td>
<td>Twice</td>
<td>500 to 1,000</td>
</tr>
<tr>
<td>Normal</td>
<td>&gt; 80</td>
<td>Twice</td>
<td>500 to 1,500</td>
</tr>
</tbody>
</table>

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

\[
\text{CL}_{cr} = \frac{\text{weight (kg) x [140 - age (years)]}}{0.8136 \times \text{serum creatinine (mg/dL)}} \times 0.85 \text{ for women}
\]

Using (BSA) body surface area the CL<sub>cr</sub> is adjusted using the following formulation:

\[
\text{CL}_{cr} \text{ (mL/min/1.73m}^2) = \frac{1.73 \times \text{CL}_{cr} \text{ (mL/min)}}{\text{BSA subject (m}^2)}
\]

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 creatinine clearance is < 60 mL/min/1.73 m², 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 Everet tablets or oral solution (see section 6.1).
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.

Everet oral solution contains methylhydroxybenzoate and propylhydroxybenzoate which may cause allergic reactions (possibly delayed) and maltitol which may have a mild laxative effect. Everet oral solution also contains glycerol which can cause headache, stomach upset and diarrhoea when ingested in doses greater than 10 g. Please note, however, that the glycerol content is 1.2 g in a recommended Everet dose in children weighing 20 kg or less. Patients with rare hereditary problems of fructose intolerance should not take the oral solution.

**Suicidal behaviour and ideation**
Antiepileptic drugs, 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>
<thead>
<tr>
<th>Table 3 Risk by indication for antiepileptic drugs in the pooled analysis Indication</th>
<th>Placebo patients with events/1000 patients</th>
<th>Drug patients with events/1000 patients</th>
<th>Relative risk: incidence of events in drug patients/incidence in placebo patients</th>
<th>Risk difference: additional drug patients with events per 1000 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>1.0</td>
<td>3.4</td>
<td>3.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>5.7</td>
<td>8.5</td>
<td>1.5</td>
<td>2.9</td>
</tr>
<tr>
<td>Other</td>
<td>1.0</td>
<td>1.8</td>
<td>1.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Total</td>
<td>2.4</td>
<td>4.3</td>
<td>1.8</td>
<td>1.9</td>
</tr>
</tbody>
</table>
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.

**Patients with impaired renal function**

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).

**4.5 Interaction with other medicines and other forms of interaction**

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 P<sub>450</sub> 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 probenecid interacting with levetiracetam was not studied and the effect of levetiracetam on other actively secreted drugs *e.g.* 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 antiepileptic medicines (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) serum concentrations. Levetiracetam pharmacokinetics was not influenced by these antiepileptic medicinal products.

In paediatric patients receiving up to 60mg/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 antiepileptic 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 are 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 1800mg/kg/day (approximately 6 times the maximum recommended human dose on a mg/m²). 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/m² 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/m² basis). The developmental no-effect dose was 70 mg/kg/day (equivalent to 0.2 times the maximal human dose on a mg/m² 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/m² 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/m² basis). The developmental no-effect dose was 200 mg/kg/day (1.3 times the maximal human dose on a mg/m² 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/m² basis). The developmental no-effect dose was 1200 mg/kg/day (4 times the maximal human dose on a mg/m² 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/m² 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 i.e. up to 1800mg/kg/day.
As a result of antiepileptic 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) antiepileptic drugs 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;
- Four weeks prior to conception and for twelve weeks after conception, folic acid supplementation (5mg) should be taken;
- For the pregnant patient taking AED’s, specialist prenatal diagnosis together with detailed mid-trimester ultrasound should be undertaken and offered.

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 antiepileptic drugs. 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 e.g. 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 antiepileptic 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 3000 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 1023 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:**

<table>
<thead>
<tr>
<th>Body System / Adverse Event</th>
<th>Number of placebo patients = 351</th>
<th>Number of patients treated with Levetiracetam = 672</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percentage (%)</td>
<td>Percentage (%)</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>9.7</td>
<td>14.9</td>
</tr>
<tr>
<td>Whole Body</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accidental Injury</td>
<td>16.5</td>
<td>10.3</td>
</tr>
<tr>
<td>Headache</td>
<td>13.7</td>
<td>13.1</td>
</tr>
<tr>
<td>Asthenia</td>
<td>9.7</td>
<td>14.1</td>
</tr>
<tr>
<td>Infection</td>
<td>7.4</td>
<td>13.2</td>
</tr>
</tbody>
</table>

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 10⁶/mm²) 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 10⁹/L) decreased neutrophil count and 3.2% of treated and 1.8% of placebo patients had at least one possibly significant (≤2.8 x 10⁹/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:

<table>
<thead>
<tr>
<th>Body System / Adverse Event</th>
<th>Number of placebo patients = 351</th>
<th>Number of patients treated with Levetiracetam = 672</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percentage (%)</td>
<td>Percentage (%)</td>
</tr>
<tr>
<td><strong>Nervous system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amnesia</td>
<td>0.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.1</td>
<td>1.6</td>
</tr>
<tr>
<td>Ataxia</td>
<td>1.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Convulsion</td>
<td>6.8</td>
<td>6.0</td>
</tr>
<tr>
<td>Depression</td>
<td>2.3</td>
<td>4.0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4.3</td>
<td>9.2</td>
</tr>
<tr>
<td>Emotional Lability</td>
<td>0.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2.8</td>
<td>3.0</td>
</tr>
<tr>
<td>Nervousness</td>
<td>1.7</td>
<td>3.9</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>1.7</td>
<td>1.9</td>
</tr>
<tr>
<td>Thinking abnormal</td>
<td>1.4</td>
<td>1.5</td>
</tr>
<tr>
<td>Tremor</td>
<td>1.7</td>
<td>1.5</td>
</tr>
<tr>
<td>Vertigo</td>
<td>1.4</td>
<td>2.5</td>
</tr>
<tr>
<td><strong>Digestive System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>2.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>5.1</td>
<td>4.2</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>3.4</td>
<td>2.8</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>0.9</td>
<td>1.2</td>
</tr>
<tr>
<td>Gingivitis</td>
<td>0.6</td>
<td>1.2</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.6</td>
<td>4.2</td>
</tr>
<tr>
<td>Tooth Disorder</td>
<td>0.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.0</td>
<td>2.2</td>
</tr>
<tr>
<td><strong>Whole Body</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>5.1</td>
<td>3.7</td>
</tr>
<tr>
<td>Back Pain</td>
<td>4.6</td>
<td>4.0</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>1.1</td>
<td>1.3</td>
</tr>
<tr>
<td>Drug Level Increased</td>
<td>0.9</td>
<td>1.3</td>
</tr>
<tr>
<td>Fever</td>
<td>1.7</td>
<td>1.3</td>
</tr>
<tr>
<td>Flu Syndrome</td>
<td>6.0</td>
<td>4.2</td>
</tr>
<tr>
<td>Hostility</td>
<td>0.6</td>
<td>2.1</td>
</tr>
<tr>
<td>Pain</td>
<td>6.6</td>
<td>6.5</td>
</tr>
<tr>
<td><strong>Nutritional/Metabolic Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight gain</td>
<td>1.1</td>
<td>1.2</td>
</tr>
<tr>
<td><strong>Lymph and Haemic System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>1.1</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Skin and Appendages</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>4.0</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>Urogenital System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>3.4</td>
<td>1.9</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Body System / Adverse Event</th>
<th>Number of placebo patients = 97 Percentage (%)</th>
<th>Number of patients treated with Levetiracetam = 101 Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nervous System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>11</td>
<td>23</td>
</tr>
<tr>
<td>Hostility</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Nervousness</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Personality Disorder</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Emotional Lability</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Agitation</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Depression</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Vertigo</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Reflexes Increased</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Confusion</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>
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, thinking abnormal, 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 and attempted suicide.

**Blood and lymphatic system disorders**: Neutropenia, pancytopenia with bone marrow suppression identified in some cases, and agranulocytosis, leucopenia.

**Bilary and Liver disorders**: Abnormal liver function test, hepatitis, and hepatic failure.

**Nutritional and Metabolic disorders**: Pancreatitis, hyponatremia, 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, lethargy

**Immune system disorders**: drug reaction with eosinophilia and systemic symptoms (DRESS)

**Musculoskeletal and connective tissue disorders**: muscular weakness

**Renal and urinary disorders**: acute kidney injury

**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://nzphvc.otago.ac.nz/reporting/](https://nzphvc.otago.ac.nz/reporting/).

**4.9 Overdose**

In the clinical development program, the highest known dose of levetiracetam received was 6000mg/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 cases 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 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: antiepileptics, other antiepileptics, ATC code: N03AX14.

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 anti-epileptic drugs (AED’s). 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 affect 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 antiepileptic mechanism of action may be due to interaction with SV2A (synaptic vesicle protein 2A).

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

Structural formula

Empirical formula: C₈H₁₄N₂O₂
Molecular weight: 170.21

Levetiracetam is chemically unrelated to existing antiepileptic drugs (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 (5.7g/100mL), soluble in ethanol (16.5g/100mL) and in methanol (53.6g/10mL), and freely soluble in chloroform (65.3g/100mL) and in water (104g/100mL). CAS-102767-28-2 and structure indicated above:

Clinical Trials
Effectiveness in Partial Onset Seizures in Adult Patients with Epilepsy.
The effectiveness of levetiracetam as adjunctive therapy (added to other antiepileptic drugs) 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.**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=95)</th>
<th>Levetiracetam 1000 mg/day (N=97)</th>
<th>Levetiracetam 3000 mg/day (N=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent reduction in partial seizure frequency over placebo</td>
<td>-</td>
<td>26.1% P&lt;0.001</td>
<td>30.1% P&lt;0.001</td>
</tr>
</tbody>
</table>

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**

![Graph showing responder rates](image)

*P<0.001 versus placebo

**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

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=111)</th>
<th>Levetiracetam 1000 mg/day (N=106)</th>
<th>Levetiracetam 2000 mg/day (N=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent reduction in partial seizure frequency over placebo</td>
<td>-</td>
<td>17.1%</td>
<td>21.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P≤ 0.001</td>
<td>P≤ 0.001</td>
</tr>
</tbody>
</table>

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.**

![Graph showing responder rate](image)

*P<0.001 versus placebo

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.**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=104)</th>
<th>Levetiracetam 3000 mg/day (N=180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent reduction in partial seizure frequency over placebo</td>
<td>-</td>
<td>23.0% P&lt;0.001</td>
</tr>
</tbody>
</table>

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.**

*P<0.001 versus placebo

**Effectiveness in Partial Onset Seizures in Paediatric Patients with Epilepsy.**

The effectiveness of levetiracetam as adjunctive therapy (added to other antiepileptic drugs) in paediatric patients was established in a multicenter, randomized 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 antiepileptic drugs (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 randomized 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 generalized. 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 randomized 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**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=97)</th>
<th>Levetiracetam (N=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent reduction in partial seizure frequency over placebo</td>
<td>-</td>
<td>26.8% P=0.0002</td>
</tr>
</tbody>
</table>

The percentage of patients (y-axis) who ≥ 50% reduction in weekly seizure rates from baseline in partial onset seizure frequency over the entire randomized 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)**

![Figure 4: Responder Rate (≥ 50% Reduction from Baseline)](image)

*P<0.0002 versus placebo

**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 juvenile myoclonic epilepsy experiencing myoclonic seizures was established in one multicenter, randomised, double-blind, placebo controlled study, conducted at 37 sites in 14 countries. Eligible patients on a stable dose of 1 antiepileptic drug (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 idiopathic generalised epilepsy 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

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=60)</th>
<th>Levetiracetam (N=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of responders</td>
<td>23.3%</td>
<td>58.3%*</td>
</tr>
</tbody>
</table>

*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 antiepileptic drugs) in patients 4 years of age and older with idiopathic generalised epilepsy experiencing primary generalised tonic-clonic (PGTC) seizures was established in one multicenter, randomised, double-blind, placebo-controlled study, conducted at 50 sites in 8 countries. Eligible patients on a stable dose of 1 or 2 antiepileptic drugs (AEDs) experiencing at least 3 PGTC seizures during the 8-week combined baseline period (at least one PGTC seizure during the 4 weeks prior to the prospective baseline period and at least one 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 idiopathic generalised epilepsy (predominately juvenile myoclonic epilepsy, juvenile absence epilepsy, childhood absence epilepsy, or epilepsy with Grand Mal seizures on awakening) experiencing primary generalised tonic-clonic seizures. Each of these syndromes of idiopathic generalised epilepsy 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 pediatric 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 Median Percent Reduction from Baseline In PGTC Seizure Frequency Per Week

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=84)</th>
<th>Levetiracetam (N=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent reduction in PGTC seizure frequency</td>
<td>44.6%</td>
<td>77.6%*</td>
</tr>
</tbody>
</table>

*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.
When levetiracetam was used to treat primary generalised tonic-clonic seizures in adults and adolescents with idiopathic generalised epilepsy, 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 1500mg 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 1.6 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).

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 ($C_{\text{max}}$) are reached. After a twice daily administration schedule for two days, steady state is achieved. ($C_{\text{max}}$) peak concentrations are typically 31µg/mL following a single 1000 mg dose and 43µg/mL following repeated 1000mg 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 to 0.7L/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 P<sub>450</sub> 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 P<sub>450</sub> isoforms (CYP3A4, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP1A2), exopoxide 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 (680µg/mL), although at concentrations approximating C<sub>max</sub> after repeated 1500mg 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.

**Elimination**

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. 0.96mL/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 0.6mL/min/kg, which indicates that levetiractam 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**

Everet (REX Medical): 6 September 2018  Page 21
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 (refer Dosage and Administration).

**Children (4 to 12 years of age)**

In epileptic children (6 to 12 years of age) after a single dose of 20mg/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 20mg to 60mg/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 1.1mL/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 (20mg/kg) approx 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 (1.5mL/min/kg) versus adults (0.96mL/min/kg).

**Renal impairment**

Levetiracetam and its major metabolite ucbl057 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 Dosage and Administration).

In adult patients with anuric end stage renal disease, the half life was approx 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 Dosage and Administration).

**5.3 Preclinical safety data**

**Carcinogenesis**

There was no evidence of carcinogenicity in rats that were given levetiracetam in the diet for 104 weeks at doses of 50, 300 and 1800mg/kg/day. The highest dose corresponds to 3000mg on a mg/m² basis, which is approximately 6 times the maximum recommended daily human dose (MRHD) of 3000mg and it also provided systemic exposure (AUC) approximately 6 times that achieved in humans receiving the MRHD.

A study was conducted in which mice received levetiracetam in the diet for 80 weeks at doses of 60, 240 and 960mg/kg/day where the high dose is equivalent to 2 times the MRHD on a mg/m² or exposure basis. No evidence for carcinogenicity was seen in this study.

A further study was completed at the higher dose rates in mice using oral gavage for 2 years at 1000, 2000 and 4000mg/kg/day. This high dose of 4000mg/kg/day was reduced to 3000mg/kg/day due to poor survival. 3000mg/kg/day is equivalent to 12 times the MHRD. No evidence of carcinogenicity was seen in this study.
Genotoxicity
In gene mutation studies, levetiracetam was negative in the bacterial Chinese hamster ovary/HGPRT locus assay. Levetiracetam was also negative in chromosomal damage in vitro and in vivo (using Chinese hamster ovary cells, mouse nucleus test). The major metabolite of levetiracetam, (ucb L057 and the hydrolysis product), was not mutagenic in the in vitro mouse lymphoma study or mutagenic in the bacterial reverse mutation assays.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Excipients
Everet 250 mg film coated tablets contain corn starch, povidone, purified water, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, Opadry 03B50643 blue coloured coating.

Everet 500 mg film coated tablets contain corn starch, povidone, purified water, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, Opadry 03B52573 yellow coloured coating.

Everet 750 mg film coated tablets contain corn starch, povidone, purified water, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, Opadry 03B54276 pink coloured coating.

Everet 1000 mg film coated tablets contain corn starch, povidone, purified water, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, Opadry 04F58804 white coloured coating.

Everet oral solution contains the following excipients: Sodium citrate dihydrate, citric acid monohydrate, methylhydroxybenzoate, propylhydroxybenzoate, glycerol, maltitol solution, acesulfame potassium, Monoammonium glycyrrhizinate, grape flavour and purified water.

Everet tablets do NOT contain gluten or lactose.

6.2 Incompatibilities
None known.

6.3 Shelf life
Shelf life is 36 months (3 years) from manufacture.

6.4 Special precautions for storage
Everet tablets and oral solution should be stored at or below 25°C. Once opened, Everet oral solution should be discarded after 90 days.

6.5 Nature and contents of container
Everet 250mg film coated tablets are available in PVC/PE/PVDC/Al blisters of 60 tablets.
Everet 500mg film coated tablets are available in PVC/PE/PVDC/Al blisters of 60 tablets.
Everet 750mg film coated tablets are available in PVC/PE/PVDC/Al blisters of 60 tablets.
Everet 1000mg film coated tablets are available in PVC/PE/PVDC/Al blisters of 60 tablets.

Everet 100 mg/ml oral solution is available in amber glass bottles of 300 ml with a child resistant closure. The pack also contains a 10 mL oral syringe with a graduation every 0.25 mL (0.25 mg) and an adaptor for the syringe.

6.6 Special precautions for disposal
No special requirements.

7 MEDICINE SCHEDULE
Prescription Medicine.

8 SPONSOR
REX Medical Limited
PO Box 18-119
Glen Innes
Auckland 1743

Telephone:  (09) 574 6060
Fax:  (09) 574 6070

9 DATE OF FIRST APPROVAL
250 mg, 500 mg, 750 mg tablets: 22 July 2010
1000 mg tablets: 19 December 2013
Oral Solution: 25 October 2018

10 DATE OF REVISION OF THE TEXT
6 September 2018
### SUMMARY TABLE OF CHANGES

<table>
<thead>
<tr>
<th>Section changed</th>
<th>Summary of new information</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.8</td>
<td>Reporting of adverse events added</td>
</tr>
<tr>
<td>4.9</td>
<td>Poison information centre contact added</td>
</tr>
<tr>
<td>6.6</td>
<td>Section added</td>
</tr>
</tbody>
</table>