AUSTRALIAN PRODUCT INFORMATION

KEPPRA (LEVETIRACETAM)
FILM-COATED TABLETS AND ORAL SOLUTION

1 NAME OF THE MEDICINE

Levetiracetam

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Keppra film-coated tablets are available in strengths of 250 mg, 500 mg, 750 mg and 1000 mg levetiracetam. Keppra oral solution is available as 100 mg/mL strength.

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

Keppra oral solution contains the following excipients: Methylhydroxybenzoate, propylhydroxybenzoate, and maltitol solution. For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Keppra film-coated tablets:

250 mg. Blue, oblong, scored film-coated tablet debossed with the code ucb and 250 on one side.

500 mg. Yellow, oblong, scored film-coated tablet debossed with the code ucb and 500 on one side.

750 mg.* Orange, oblong, scored film-coated tablet debossed with the code ucb and 750 on one side.

1000 mg. White, oblong, scored film-coated tablet debossed with the code ucb and 1000 on one side.

**not currently distributed in Australia.*

Keppra 100 mg/mL oral solution is a clear liquid.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Keppra (film-coated tablets and 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); and
- 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

Keppra therapy can be initiated with either intravenous or oral administration. Conversion to or from oral to intravenous can be done directly without titration. The total daily dose and frequency of administration should be maintained.

The film-coated tablets must be taken orally, 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. After oral administration the bitter taste of levetiracetam may be experienced. The daily dose is administered in two equally divided doses.

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 Keppra 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 with compromised renal function (see Patients with renal impairment below).

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.

The dosage in children 50 kg or greater is the same as in adults.

The physician should prescribe the most appropriate pharmaceutical form and strength according to weight and dose.

Table 1. Recommended dosing in children aged 4 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 Keppra 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
The Keppra daily dose must be individualised according to renal function. For adult patients, see Table 2 and adjust the dose as indicated.

To use this dosing table, 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 (micromol/L) determination using the following formula:

$$CLcr = \frac{[140\text{-age(years)}] \times \text{weight (kg)}}{0.8136 \times \text{serum creatinine (}\mu\text{mol/L)}} \text{ (x 0.85 for women)}$$

Then CLcr is adjusted for body surface area (BSA) as follows:

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

Table 2. Adult dosage schedule based on renal function.

Group	Creatinine clearance (mL/min/1.73m^2)	Dosage (mg)	Frequency (daily)
Normal	≥ 80	500 to 1500	Twice
Mild	50-79	500 to 1000	Twice
Moderate	30-49	250 to 750	Twice
Severe	< 30	250 to 500	Twice
End-stage renal disease patients undergoing dialysis [(1)]	-	500 to 1000	Once [(2)]

[(1)] A 750 mg loading dose is recommended on the first day of treatment with levetiracetam.
[(2)] Following dialysis, a 250 to 500 mg supplemental dose is recommended.

For children with renal impairment, levetiracetam dose needs to be adjusted based on the renal function as levetiracetam clearance is related to renal function. This recommendation is based on a study in adult renally impaired patients.

Patients with hepatic impairment
No dose adjustment is needed in patients with mild and moderate hepatic impairment.

In patients with severe hepatic impairment, the creatinine clearance may underestimate the renal insufficiency. Therefore a 50% reduction of the daily maintenance dose is recommended when the creatinine clearance is < 60 mL/min/1.73 m^2.

4.3 CONTRAINDICATIONS

Hypersensitivity to levetiracetam or other pyrrolidone derivatives or any of the excipients (see Section 6.1 List of Excipients).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

In accordance with current clinical practice, if Keppra has to be discontinued it is recommended to withdraw it gradually.

Amongst its excipients, Keppra oral solution includes methylhydroxybenzoate and propylhydroxybenzoate which may cause allergic reactions (possibly delayed) and maltitol which may have a mild laxative effect. Keppra 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 less than 1.5 g in a recommended Keppra dose in children weighing 20 kg or less. Patients with rare hereditary problems of fructose intolerance should not take the oral solution.

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.

No data on the interaction of levetiracetam with alcohol are available.

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 3. Risk by indication for antiepileptic drugs in the pooled analysis

Indication	Placebo patients with events/1000 patients	Drug patients with events/1000 patients	Relative Risk: Incidence of events in Drug patients/incidence in Placebo patients	Risk Difference: Additional Drug patients with events per 1000 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.

Psychiatric reactions and changes in behaviour
Levetiracetam may cause changes in behaviour (e.g. aggression, agitation, anger, anxiety, apathy, depression, hostility, and irritability) and psychotic symptoms. Patients treated with levetiracetam should be monitored for psychiatric signs and symptoms.

Seizure Worsening
A paradoxical reaction of worsening of seizure may be observed especially when starting treatment or at increase in dose.
Lack of efficacy or seizure worsening has been reported in patients with epilepsy associated with SCN8A mutations.

Blood cell count
Cases of decreased blood cell counts (neutropenia, agranulocytosis, leucopenia, thrombocytopenia and pancytopenia) have been described in association with levetiracetam administration. Complete

blood cell counts are advised in patients experiencing important weakness, pyrexia, recurrent infections or coagulation disorders (See Section 4.8 Adverse effects (undesirable effects)).

Use in hepatic impairment
See section 4.2 Dose and Method of Administration and Section 5.3 Pharmacokinetic Properties.

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

Use in the elderly
See section 4.2 Dose and Method of Administration and Section 5.3 Pharmacokinetic Properties.

Paediatric use
To date, there are no data to support the use of levetiracetam in patients less than 4 years of age.

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

In vitro, levetiracetam and its major metabolite (ucb L057) have been shown not to inhibit the major human liver cytochrome P450 isoforms, glucuronyl transferase, (valproic acid) and epoxide hydroxylase activities. In human hepatocytes in culture, levetiracetam did not cause enzyme induction.

Probenecid (500 mg four times daily) has been shown to inhibit the renal clearance of the major metabolite (ucb L057) but not levetiracetam. Nevertheless, the concentration of ucb L057 remains low. It is expected that other drugs excreted by active tubular secretion could also reduce the renal clearance of the metabolite. The effect of levetiracetam on probenecid was not studied and the effect of levetiracetam on other actively secreted drugs, e.g. NSAIDs, sulphonamides, and methotrexate is unknown.

Premarketing data from clinical studies conducted in adults indicate that Keppra did not influence the serum concentrations of existing antiepileptic medicinal products (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these antiepileptic medicinal products did not influence the pharmacokinetics of Keppra.

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

A retrospective assessment of pharmacokinetic interactions in children and adolescents with epilepsy (4 to 17 years) confirmed that adjunctive therapy with levetiracetam did not influence the steady-state serum concentrations of concomitantly administered carbamazepine, valproate, topiramate and lamotrigine. However, data suggested that enzyme inducing antiepileptic medicinal products increase levetiracetam clearance by 22%. Dosage adjustment is not required.

Pharmacokinetic studies demonstrated a lack of interaction with digoxin, oral contraceptives

(ethinylestradiol and levonorgestrel) and warfarin. Endocrine parameters (LH and progesterone) and prothrombin times were not modified.

No data on the influence of antacids on the absorption of levetiracetam are available.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
There are no human data on the effects of Keppra on male or female fertility. No adverse effects on male or female fertility or reproductive performance were observed in rats at oral doses of levetiracetam up to 1800 mg/kg/day (corresponding to approximately 6 times the maximal recommended clinical dose on a mg/m^2 basis) administered for at least two weeks prior to, and throughout, mating.

Use in pregnancy
(Category B3)

In rats and rabbits, levetiracetam and/or its metabolites cross the placenta and the foetal levels approximate maternal plasma levels. In these species, levetiracetam produced evidence of developmental toxicity at doses similar to or greater than human therapeutic doses.

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 prenatally 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).

Neonatal and juvenile animal studies in rats and dogs demonstrated that there were no adverse effects seen in any of the standard developmental or maturation endpoints at doses of up to 1800 mg/kg/day corresponding to 30 times the maximum recommended human dose.
The risk of having an abnormal child as a result of antiepileptic medication is far outweighed by the dangers to the mother and foetus of uncontrolled epilepsy.

It is recommended that:

- women on antiepileptic drugs (AEDs) receive prepregnancy counselling with regard to the risk of foetal abnormalities;
- AEDs should be continued during pregnancy and monotherapy should be used if possible at the lowest effective dose as risk of abnormality is greater in women taking combined medication;
- folic acid supplementation (5 mg) should be commenced four weeks prior to and continue for twelve weeks after conception;
- specialist prenatal diagnosis including detailed midtrimester ultrasound should be offered.
- As with all antiepileptic medicines, sudden discontinuation of levetiracetam should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child.

A large amount of postmarketing data on pregnant women exposed to levetiracetam monotherapy (more than 1800, among which in more than 1500 exposure occurred during the 1st trimester) do not suggest an increase in the risk of major congenital malformations.

Limited evidence is available on the neurodevelopment of children exposed to levetiracetam monotherapy in utero. Information available from published epidemiological studies does not suggest an increased risk of neurodevelopmental disorders or delays.

Generally, therapy with multiple antiepileptic drugs (including polytherapy containing levetiracetam) is associated with a higher risk of major malformations than monotherapy.

Keppra should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. As with other antiepileptic drugs, physiological changes during pregnancy may affect levetiracetam concentration. A decrease in levetiracetam plasma concentrations has been observed during pregnancy. This decrease is more pronounced during the third trimester (up to 60% of baseline concentration before pregnancy). Appropriate clinical management of pregnant women treated with levetiracetam should be ensured. To monitor the outcome of pregnancy in women exposed to Keppra, doctors are encouraged to register pregnant patients taking Keppra on the Australian Pregnancy Register for Women on Antiepileptic Medication with Epilepsy and Allied Conditions by calling 1800 069 722.

Use in lactation
Levetiracetam and/or its metabolites are excreted in milk in lactating rats; peak milk concentrations occurred 3 hours after oral administration (milk: plasma ratio 0.9). Levetiracetam is excreted in human breast milk. Because of the potential for serious adverse reactions in breastfeeding infants from Keppra, a decision should be made whether to discontinue breastfeeding or discontinue the drug, taking into account the importance of the drug to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. Due to possible different individual sensitivity, some patients might experience, at the beginning of treatment or following a dosage increase, somnolence or other CNS related symptoms. Therefore, caution is recommended in those patients when performing skilled tasks, e.g. driving vehicles, or operating machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The prescriber should be aware that following data were obtained from studies where Keppra was added to concomitant antiepileptic therapy. Therefore it was not possible in all cases to determine which agent(s), if any, was associated with adverse events. It is also difficult to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies.

Adult patients
Keppra has been administered to more than 3000 subjects and patients. Of these, 780 patients were treated for more than 6 months, 592 for more than 1 year, 366 for more than 2 years and 185 for more than 3 years.

1023 adult patients with epilepsy participated in controlled clinical trials (672 patients were treated with levetiracetam and 351 patients with placebo).

From placebo controlled studies conducted in adults, 46.4% and 42.2% of patients experienced drug related treatment emergent adverse events in the levetiracetam group and placebo group, respectively. 2.4% and 2.0% of patients experienced serious drug related treatment emergent adverse events in the levetiracetam group and placebo group, respectively.

During monotherapy treatment with levetiracetam, 79.6% of subjects experienced at least one adverse event and 49.8% experienced at least one drug related undesirable effect. The most frequently reported adverse effects were fatigue and somnolence.

Very common adverse events (≥ 10%)
The very common adverse events (≥ 10%) were somnolence, asthenia, infection, headache and accidental injury. Of these, somnolence, asthenia and infection appeared to occur more frequently in levetiracetam treated patients than in placebo treated patients, whereas accidental injury was more common in the placebo group and headache was similarly reported in the two groups. (See Table 4).

Table 4. Incidence (%) of very common treatment-emergent adverse events in adult placebo-controlled studies, by body system

Body System / Adverse Event	KEPPRA group (N=672) %	Placebo group (N=351) %
Body as a Whole		
Accidental Injury	10.3	16.5
Asthenia	14.1	9.7
Headache	13.1	13.7
Infection	13.2	7.4
Nervous System		
Somnolence	14.9	9.7

In the pooled safety analysis, there was no clear dose response relationship but incidence and severity of CNS related undesirable effects decreased over time.

More than 93% of events categorised under the COSTART preferred term infection are symptoms of community acquired infections (common cold and upper respiratory tract infections). There was no increase in incidence of other infections (lower respiratory tract infections, urinary tract infections, etc.). Minor, but statistically significant, decreases compared to placebo in total mean RBC count ($0.03 \times 10^6/mm^2$), mean hemoglobin (0.9 g/L), and mean haematocrit (0.38%) were seen in Keppra treated patients in controlled trials. A total of 3.2% of treated and 1.8% of placebo patients had at least one possibly significant ($\leq 2.8 \times 10^9$/L) decreased WBC, and 2.4% for treated and 1.4% of placebo patients had at least one possible significant ($\leq 1.0 \times 10^9$/L) decreased neutrophil count. Of the treated patients with a low neutrophil count, all but one rose towards or to baseline with continued treatment. No patient was discontinued secondary to low neutrophil counts.

Common adverse events (≥ 1%, < 10%)
See Table 5.

Table 5. Incidence (%) of common treatment-emergent adverse events in adult placebo-controlled studies, by body system

Body System / Adverse Event	KEPPRA group (N=672) %	Placebo group (N=351) %
BODY AS A WHOLE		
Abdominal Pain	3.7	5.1
Back Pain	4.0	4.6
Chest Pain	1.3	1.1
Drug Level Increased	1.3	0.9
Fever	1.3	1.7
Flu Syndrome	4.2	6.0
Hostility	2.1	0.6
Pain	6.5	6.6
DIGESTIVE SYSTEM		
Anorexia	2.4	2.0
Diarrhoea	4.2	5.1
Dyspepsia	2.8	3.4
Gastroenteritis	1.2	0.9
Gingivitis	1.2	0.6
Nausea	4.2	4.6
Tooth Disorder	1.5	0.6
Vomiting	2.2	2.0
HAEMIC AND LYMPH SYSTEM		
Ecchymosis	1.5	1.1
METABOLIC / NUTR DIS		
Weight gain	1.2	1.1
NERVOUS SYSTEM		
Amnesia	1.6	0.3
Anxiety	1.6	1.1
Ataxia	2.5	1.4
Convulsion	6.0	6.8
Depression	4.0	2.3
Dizziness	9.2	4.3
Emotional Lability	1.6	0.3
Insomnia	3.0	2.8

Body System / Adverse Event	KEPPRA group (N=672) %	Placebo group (N=351) %
Nervousness	3.9	1.7
Paraesthesia	1.9	1.7
Thinking abnormal	1.5	1.4
Tremor	1.5	1.7
Vertigo	2.5	1.4
RESPIRATORY SYSTEM		
Bronchitis	1.3	1.4
Cough Increased	2.1	1.7
Pharyngitis	5.7	3.7
Rhinitis	4.3	2.6
Sinusitis	2.1	0.9
SKIN AND APPENDAGES		
Rash	2.8	4.0
SPECIAL SENSES		
Amblyopia	1.2	1.4
Diplopia	2.4	1.7
Otitis media	1.2	0.9
UROGENITAL SYSTEM		
Urinary Tract Infection	1.9	3.4

The incidence of serious adverse events in placebo controlled studies was 9.9% in the levetiracetam group versus 8.9% in the placebo group. Many of the serious adverse events are typical for a population of patients with epilepsy.

The serious adverse events which occurred in more than 1% of patients were convulsion (1.8% in levetiracetam group versus 1.4% in placebo group) and accidental injury (1.6% in both levetiracetam and placebo group).

Paediatric patients

A study conducted in paediatric patients (4 to 16 years of age) showed that 55.4% and 40.2% of the paediatric patients experienced undesirable effects in the Keppra and placebo groups, respectively, and that 0.0% and 1.0% of the paediatric patients experienced serious undesirable effects in the Keppra and placebo groups, respectively. In the paediatric clinical study, 16.8% of patients receiving Keppra and 20.6% receiving placebo either discontinued or had a dose reduction as a result of an adverse event.The most commonly reported undesirable effects in the paediatric population were somnolence, hostility, nervousness, emotional lability, agitation, anorexia, asthenia and headache. Safety results in paediatric patients were consistent with the safety profile of levetiracetam in adults, except for behavioural and psychiatric undesirable effects which were more common in children than in adults (38.6% versus 18.6%). However, the relative risk was similar in children as compared to adults as there was also a higher incidence of behavioural psychiatric adverse events in the placebo group in children as compared to adults (27.8% versus 10.5%). (See Table 6).

Table 6. Incidence (%) of treatment-emergent adverse events in a placebo-controlled, add-on study in paediatric patients aged 4-16 years, by body system (adverse events occurred in at least 2% of Keppra-treated patients and occurred more frequently than placebo-treated patients)

Body System / Adverse Event	KEPPRA group (N=101) %	Placebo group (N=97) %
BODY AS A WHOLE		

Body System / Adverse Event	KEPPRA group (N=101) %	Placebo group (N=97) %
Accidental Injury	17	10
Asthenia	9	3
Pain	6	3
Flu Syndrome	3	2
Face Oedema	2	1
Neck Pain	2	1
Viral Infection	2	1
DIGESTIVE SYSTEM		
Vomiting	15	13
Anorexia	13	8
Diarrhoea	8	7
Gastroenteritis	4	2
Constipation	3	1
HAEMIC AND LYMPH SYSTEM		
Ecchymosis	4	1
METABOLIC / NUTR DIS		
Dehydration	2	1
NERVOUS SYSTEM		
Somnolence	23	11
Hostility	12	6
Nervousness	10	2
Personality Disorder	8	7
Dizziness	7	2
Emotional Lability	6	4
Agitation	6	1
Depression	3	1
Vertigo	3	1
Reflexes Increased	2	1
Confusion	2	0
RESPIRATORY SYSTEM		
Rhinitis	13	8
Cough Increased	11	7
Pharyngitis	10	8
Asthma	2	1
SKIN AND APPENDAGES		
Pruritis	2	0
Skin Discolouration	2	0
Vesiculobullous Rash	2	0
SPECIAL SENSES		
Conjunctivitis	3	2
Amblyopia	2	0
Ear Pain	2	0
UROGENITAL SYSTEM		
Albuminuria	4	0
Urine Abnormality	2	1

Other events occurring in 2% or more of paediatric patients treated with Keppra but as or more frequent in the placebo group were the following: abdominal pain, allergic reaction, ataxia, convulsion, epistaxis, fever, headache, hyperkinesia, infection, insomnia, nausea, otitis media, rash, sinusitis, status epilepticus (not otherwise specified), thinking abnormal, tremor, and urinary incontinence.

Other controlled clinical trials

The following adverse effects, listed by body system, have been observed in additional controlled

clinical trials.

General disorders: Very common: fatigue.

Respiratory system: Common: nasopharyngitis.

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

Skin and subcutaneous tissue disorders: Common: eczema, pruritus.

Eye disorders: Common: vision blurred.

Blood and lymphatic system disorders: Common: thrombocytopenia.

Musculoskeletal and connective tissue disorders: Common: myalgia.

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

Postmarketing experience
In postmarketing experience, nervous system and psychiatric disorders have been most frequently reported.

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported in postmarketing experience. Data are insufficient to support an estimate of their incidence in the population to be treated.

Blood and lymphatic system disorders: Pancytopenia with bone marrow suppression identified in some of these cases, agranulocytosis, leucopenia and neutropenia.

Cardiac disorders: Electrocardiogram QT prolonged.

Immune system disorders: Anaphylaxis, drug reaction with eosinophilia and systemic symptoms (DRESS).

Psychiatric disorders: Abnormal behaviour, aggression, anger, panic attack, confusion, hallucination, psychotic disorder, suicide, suicide attempt, suicidal ideation and delirium.

Nervous system disorders: Choreoathetosis, dyskinesia, lethargy, gait disturbance, seizures aggravated.

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis, Stevens-Johnson syndrome, angioedema, erythema multiforme and alopecia; in several alopecia cases, recovery was observed when Keppra was discontinued.

Musculoskeletal and connective tissue disorders: Muscular weakness, rhabdomyolysis and blood creatine phosphokinase increased.

Liver and biliary system disorders: Hepatitis, hepatic failure and abnormal liver function test.

Renal and urinary disorders: Acute kidney injury.

Metabolic and nutritional disorders: Weight loss, pancreatitis, hyponatraemia.

Description of selected adverse reactions
The prevalence of rhabdomyolysis and blood creatine phosphokinase increase is significantly higher in Japanese patients compared to non-Japanese patients.

Evidence also suggests a possible predisposition of the Japanese population to neuroleptic malignant syndrome (NMS).

Rare cases of QT prolongation have been seen in post-marketing surveillance.

Rare cases of development of obsessive-compulsive disorders (OCD) in patients with underlying history of OCD or psychiatric disorders have been observed in post-marketing surveillance.

Multiorgan hypersensitivity reactions (also known as Drug Reaction with Eosinophilia and Systemic Symptoms, DRESS) have been reported in patients treated with some antiepileptic medicinal products. These reactions are variable in expression, but typically present with fever and rash and can be associated with involvement of different organ systems. Potential cases have been reported rarely with levetiracetam and if multiorgan hypersensitivity reaction is suspected, levetiracetam should be discontinued.

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The highest known dose of Keppra received in the clinical development program was 6000 mg/day. Other than drowsiness, there were no adverse events in the few known cases of overdose in clinical trials. Cases of somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with Keppra overdoses in postmarketing use.

There is no specific antidote for levetiracetam. Treatment for an overdose will be symptomatic and may include haemodialysis. The dialyser extraction efficiency is 60% for levetiracetam and 74% for the major metabolite (ucb L057).

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
The precise mechanism of action by which levetiracetam induces seizure protection still remains to be fully elucidated, but appears to be unrelated to the mechanisms of current antiepileptic drugs. *In vitro* and *in vivo* experiments suggest that levetiracetam does not alter basic cell characteristics and normal neurotransmission.

In vitro studies show that levetiracetam affects intraneuronal Ca^{2+} levels by partial inhibition of N-type Ca^{2+} currents and by reducing the release of Ca^{2+} from intraneuronal stores. In addition, it partially reverses the reductions in GABA and glycine-gated currents induced by zinc and β-carbolines. Furthermore, levetiracetam has been shown in *in vitro* studies to bind to a specific site in rodent brain tissue. This binding site is the synaptic vesicle protein 2A, believed to be involved in vesicle fusion and neurotransmitter exocytosis. Levetiracetam and related analogues show a rank order of affinity for binding to the synaptic vesicle protein 2A which correlates with the potency of their antiseizure protection in the mouse audiogenic model of epilepsy. This finding suggests that the interaction between levetiracetam and the synaptic vesicle protein 2A seems to contribute to the antiepileptic mechanism of action of the drug.

Pharmacodynamics

In animals

Levetiracetam is not active in the classical screening models for anticonvulsants however induces potent protection in a broad range of animal models of partial and primary generalised seizures, with an unusually high safety margin between therapeutic doses and doses inducing adverse effects.

Levetiracetam also displays potential antiepileptogenic properties by dose dependently inhibiting the development of kindling, even after discontinuation of the active substance.

Withdrawal from chronic treatment did not decrease the seizure threshold. Anxiolytic action and an absence of undesirable effects on cognitive function have also been observed.

The major metabolite, ucb L057, is inactive in seizure models.

In man

Both partial and generalised epilepsy models (epileptiform discharge/ photoparoxysmal response) confirmed the broad spectrum preclinical pharmacological profile.

Clinical trials

Effectiveness in partial onset seizures in adults and adolescents

Monotherapy. The monotherapy study was designed as a double blind, parallel group, noninferiority comparison of Keppra and carbamazepine controlled released in patients 16 years of age or older with newly diagnosed epilepsy. The seizures were to be either unprovoked partial seizures (type IA (simple partial seizures with unimpaired consciousness), IB (complex partial seizures with impaired consciousness), or IC (partial seizures secondarily generalised (with clear focal origin)) or IIE (generalised tonic-clonic seizure (without clear focal origin)), classifiable according to the International Classification of Epileptic Seizures. The study was performed in 85 centers in 13 countries (Europe and South Africa).

At the end of the 1 week screening period, eligible subjects were stratified by seizure type (IA/IB/IC or IC/IIE without clear focal origin) and randomly assigned to receive CBZ CR (N = 291) or LEV (N = 285), for up to 121 weeks depending on response. Conservatively, a controlled release (CR) formulation of carbamazepine was used to minimise adverse effects. The maximal duration for an individual subject was 121 weeks.

After a 1 week screening period (no study drug intake), the subject was randomized and entered a 2

week up titration period to the first target daily dose (LEV 1000 mg/CBZ 400 mg), followed by a one week stabilization period and an evaluation period of 26 weeks in order to achieve a 6 month seizure freedom (primary efficacy endpoint), and followed by a maintenance period of 26 additional weeks in order to assess safety and maintenance of efficacy.

If a seizure occurred during the evaluation period, dose escalation (made over a 2 week period) to the second target daily dose (LEV 2000 mg/CBZ 800 mg) was foreseen. This was followed by a 1 week stabilization period, a new evaluation period of 26 weeks and a maintenance period of 26 additional weeks. The same was true if a seizure occurred during the evaluation period at the second dose level: dose escalation (made over a 2 week period) to the third target daily dose (LEV 3000 mg/CBZ 1200 mg), followed by a one week stabilization period, a new evaluation period of 26 weeks and a maintenance period of 26 additional weeks. Fallback option: in case a subject did not tolerate the second or third study drug target dose, he/she had the opportunity, during the evaluation or the maintenance period, to have one fallback to an intermediate dose (decrease by 200 mg/day for CBZ or by 500 mg/day for LEV) and to continue in the trial on that basis. The subject could not resume the previous dose and could not have further up-titration in case a new seizure occurred.

576 subjects were randomised. Approximately one half of the patients in each treatment group completed the study (53.6% of the patients randomised to CBZ and 54.0% of the patients randomised to LEV), similar between the two treatment groups. The distribution by seizure type categories was similar in both treatment groups, with around 86.7% of subjects lastly classified as experiencing partial seizures with clear focus origin. The majority of subjects remained at dose level 1 (81.7% of subjects randomised to CBZ and 73.4% of subjects randomised to LEV in the PP population).

The prospectively defined primary endpoint was the proportion of subjects from the PP population with 6 month seizure freedom at the last evaluated dose.

One hundred seventy three (73.0%) of the PP subjects in the LEV arm were seizure free for at least 6 months at the last evaluated dose, compared to 171 subjects (72.8%) in the CBZ arm. The adjusted absolute difference LEV and CBZ (95% two sided CI) obtained from a logistic regression model including a factor for the seizure type category as last assessed (IA/IB/IC versus IC/IIE) equalled 0.2% (-7.8%; 8.2%). The lower limit of the confidence interval (-7.8%) was above the noninferiority limit set by protocol (-15%) for this primary efficacy analysis, and therefore LEV can be considered as noninferior to CBZ on the proportion of subjects seizure free at least 6 months at the first evaluated dose in the PP population. Considering the other clinically relevant end point, 56.6% and 58.5% of subjects on LEV and CBZ respectively were seizure free for 1 year.

Add-on therapy. The effectiveness of Keppra tablets 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.

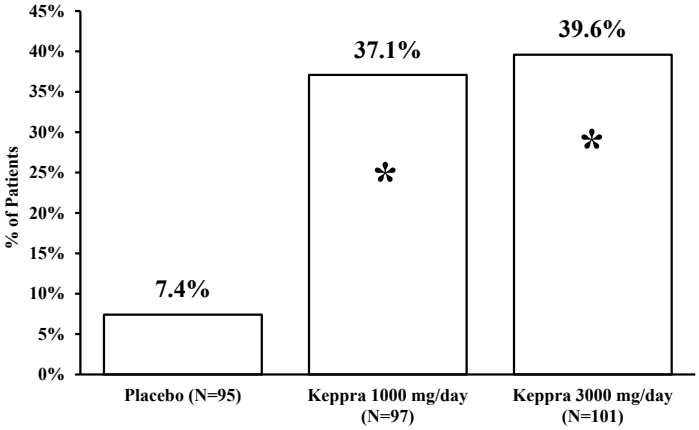
Study 1: Study 1 was a double blind, placebo controlled, parallel group study conducted at 41 sites in the United States comparing Keppra 1000 mg/day (N = 97), Keppra 3000 mg/day (N = 101) and placebo (N = 95) given in equally divided doses twice daily. After a prospective baseline period of 12 weeks, 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)	Keppra 1000 mg/day (N=97)	Keppra 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.



*P<0.001 versus placebo

Study 2: Study 2 was a double blind, placebo controlled, crossover study conducted at 62 centres in Europe comparing Keppra 1000 mg/day (N = 106), Keppra 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

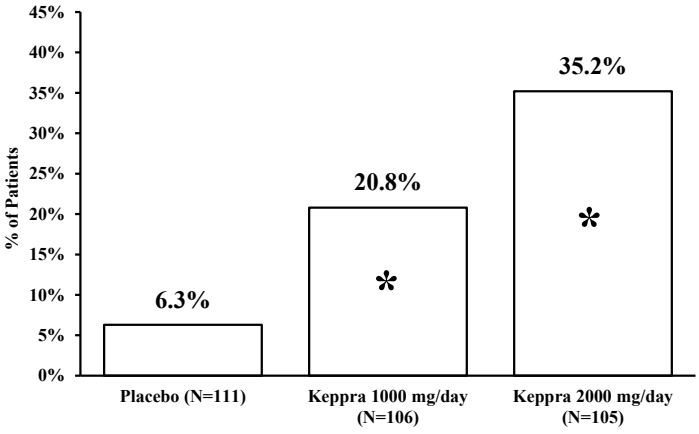
held constant. The primary measure of effectiveness was a between group comparison of the percent reduction in weekly partial seizure frequency relative to placebo over the entire randomised treatment period (titration + evaluation period). Secondary outcome variables included the responder rate (incidence 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)	Keppra 1000 mg/day (N=106)	Keppra 2000 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



*P<0.001 versus placebo

The comparison of Keppra 2000 mg/day to Keppra 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 Keppra 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).

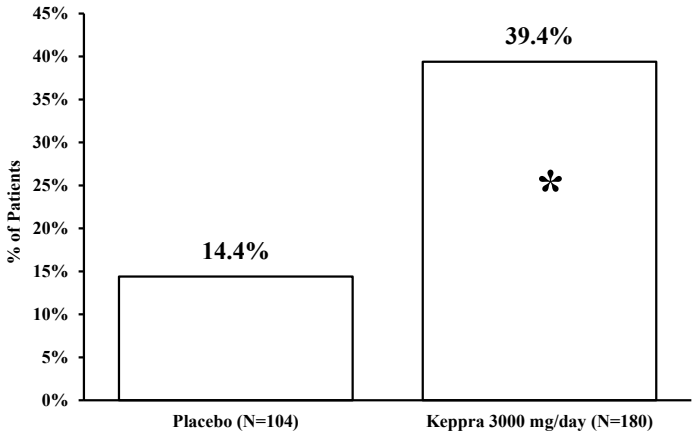
Secondary outcome variables included the responder rate (incidence of patients with ≥ 50% reduction from baseline in partial onset seizure frequency). Table 9 displays the results of the analysis of study 3.

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

	Placebo (N=104)	Keppra 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



*P<0.001 versus placebo

Effectiveness in partial onset seizures in paediatric patients with epilepsy

The effectiveness of Keppra as adjunctive therapy (added to other antiepileptic drugs) in paediatric patients was established in a multicenter, 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 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 randomised to receive either Keppra or placebo. The population included 198 patients (Keppra 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, Keppra 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 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.

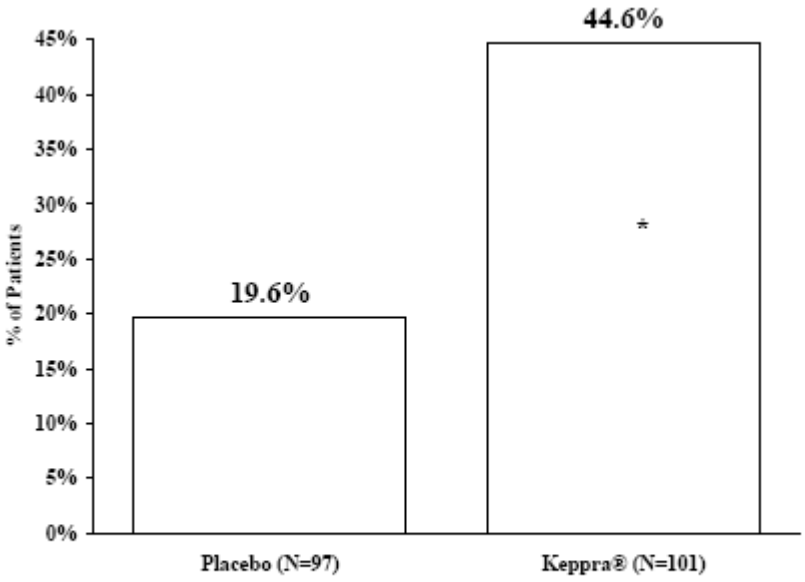
Table 10. Reduction in mean over placebo in weekly frequency of partial onset seizures

	Placebo (N=97)	Keppra (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)



*P=0.0002 versus placebo.

Effectiveness in myoclonic seizures in patients ≥ 12 years of age with juvenile myoclonic epilepsy (JME)

The effectiveness of Keppra 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 Keppra or placebo. The population included 120 patients (Keppra 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

	Placebo (N=60)	Keppra (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 Keppra 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 Keppra or placebo. The 8 week combined baseline period is referred to as baseline in the remainder of this section. The population included 164 patients (Keppra 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 Keppra and placebo treatment groups over the treatment period (titration + evaluation periods). There was a statistically significant decrease from baseline in PGTC frequency in the Keppra treated patients compared to the placebo treated patients. (See Table 12).

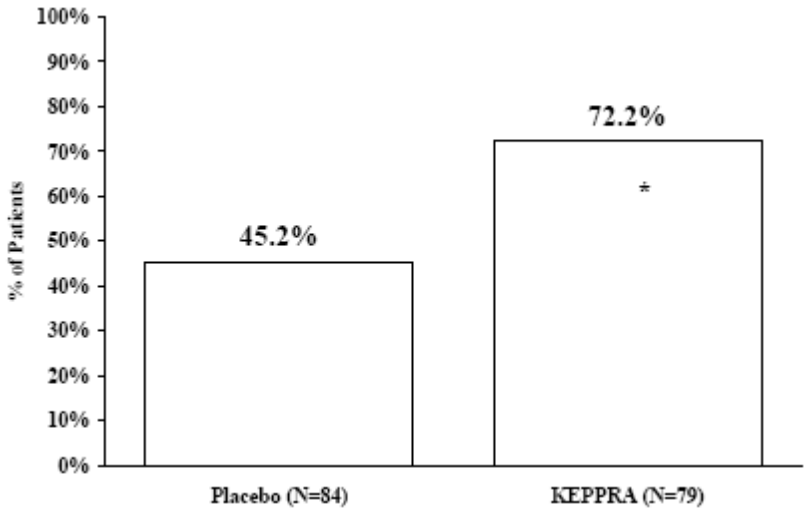
Table 12. Median Percent Reduction From Baseline In PGTC Seizure Frequency Per Week

	Placebo (N=84)	Keppra (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



*statistically significant versus placebo

When Keppra 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 highly soluble and permeable compound. The pharmacokinetic profile is linear and time independent with low intrasubject and intersubject variability. There is no modification of the clearance after repeated administration. There is no evidence for any relevant gender, race or circadian variability. The pharmacokinetic profile is comparable in healthy volunteers and in patients with epilepsy.

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.

A significant correlation between saliva and plasma concentrations has been shown in adults and children (ratio of saliva/ plasma concentrations ranged from 1 to 1.7 for oral tablet formulation and after 4 hours postdose for oral solution formulation).

A single dose of 1500 mg levetiracetam diluted in 100 mL of a compatible diluent and infused intravenously over 15 minutes is bioequivalent to 1500 mg levetiracetam oral intake, given as three 500 mg tablets.

The intravenous administration of doses up to 4000 mg diluted in 100 mL of 0.9% sodium chloride infused over 15 minutes and doses up to 2500 mg diluted in 100 mL of 0.9% sodium chloride infused over 5 minutes was evaluated. The pharmacokinetic and safety profiles did not identify any safety concerns.

Adults and adolescents

Absorption
Levetiracetam is rapidly absorbed after oral administration. Oral absolute bioavailability is close to 100%. Peak plasma concentrations (C_{max}) are achieved at 1.3 hours after dosing. Steady state is achieved after two days of a twice daily administration schedule. Peak concentrations (C_{max}) are typically 31 microgram/mL and 43 microgram/mL following a single 1000 mg dose and repeated 1000 mg b.i.d. dose respectively. The extent of absorption is dose independent and is not altered by food, but the rate of absorption is slightly reduced.

Distribution
No tissue distribution data are available in humans. Neither levetiracetam nor its major metabolite (ucb L057) are significantly bound to plasma proteins (< 10%). The volume of distribution of levetiracetam is approximately 0.5 to 0.7 L/kg, a value close to the volume of distribution of intracellular and extracellular water.

Metabolism
The major metabolic pathway (24% of the dose) is an enzymatic hydrolysis of the acetamide group. Production of this metabolite, ucb L057, is not supported by liver cytochrome P450 isoforms. Hydrolysis of the acetamide group was measurable in a large number of tissues including whole blood but not plasma. The metabolite ucb L057 is pharmacologically inactive.

Two minor metabolites were also identified. One was obtained by hydroxylation of the pyrrolidone ring (1.6% of the dose) and the other one by opening of the pyrrolidone ring (0.9% of the dose).

Other unidentified components accounted for only 0.6% of the dose.

No enantiomeric interconversion was evidenced *in vivo* for either levetiracetam or its major metabolite ucb L057.

In vitro, levetiracetam and its primary metabolite have been shown not to inhibit the major human liver cytochrome P450 isoforms (CYP3A4, 2A6, 2C9, 2C19, 2D6, 2E1 and 1A2), glucuronyl transferase (UGT1A1 and UGT1A6) and epoxide hydroxylase activities. In addition, levetiracetam does not affect the *in vitro* glucuronidation of valproic acid.

In human hepatocytes *in vitro,* levetiracetam had no effect on CYP1A1/2 or UGT isoform activities (including ethinylestradiol conjugation). Levetiracetam caused mild induction of CYP2B6 and CYP3A4, but only at high concentrations not considered to be clinically relevant. Therefore the interaction of Keppra with other substances, or vice versa, is unlikely.

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

The major route of excretion was via urine, accounting for a mean 95% of the dose, with approximately 93% of the dose excreted within 48 hours. Excretion via faeces accounted for only 0.3% of the dose. The cumulative urinary excretion of levetiracetam and its major metabolite (ucb L057) accounted for 66% and 24% of the dose respectively during the first 48 hours.

The renal clearance of levetiracetam is 0.6 mL/min/kg, indicating that it is excreted by glomerular filtration with subsequent tubular reabsorption. The renal clearance of the major metabolite, ucb L057, is 4.2 mL/min/kg indicating active tubular secretion in addition to glomerular filtration.

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

Children (4 to 12 years of age)
Following single dose administration (20 mg/kg) to epileptic children (6 to 12 years of age), the half-life of levetiracetam was 6.0 ± 1.1 hours. The apparent body clearance was approximately 30% higher than in epileptic adults.

Following repeated oral dose administration (20 to 60 mg/kg/day) to epileptic children (4 to 12 years of age), levetiracetam was rapidly absorbed. Peak plasma concentration was observed 0.5 to 1.0 hour after dosing. Linear and dose proportional increases were observed for peak plasma concentrations and area under the curve. The elimination half-life was approximately 5 hours. The apparent body clearance was 1.1 mL/min/kg.

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

Renal impairment
The apparent body clearance of both levetiracetam and its major metabolite (ucb L057) is correlated to the creatinine clearance. It is therefore recommended to adjust the maintenance daily dose of Keppra, based on creatinine clearance in patients with moderate and severe renal impairment (see Section 4.2 Dose and Method of Administration).

In anuric endstage renal disease adult subjects the half-life was approximately 25 and 3.1 hours during interdialytic and intradialytic periods respectively. The fractional removal of levetiracetam was 51% during a typical 4 hour dialysis session.

Hepatic impairment
In subjects with mild and moderate hepatic impairment, there was no relevant modification of the clearance of levetiracetam. In most subjects with severe hepatic impairment, the clearance of levetiracetam was reduced by more than 50% 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

Keppra film-coated tablets contain the following excipients: Croscarmellose sodium, macrogol 6000, silica-colloidal anhydrous, magnesium stearate and the coating specified below:

250 mg tablets: polyvinyl alcohol, titanium dioxide, macrogol 3350, talc and indigo carmine CI73015.

500 mg tablets: polyvinyl alcohol, titanium dioxide, macrogol 3350, talc and iron oxide yellow CI77492.

750 mg tablets*: polyvinyl alcohol, titanium dioxide, macrogol 3350, talc, iron oxide red CI77491 and sunset yellow FCF CI15985.

1000 mg tablets: polyvinyl alcohol, titanium dioxide, macrogol 3350 and talc.

**not currently distributed in Australia.*

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

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Keppra film-coated tablets: 2.5 years from date of manufacture.

Keppra oral solution: 3 years from date of manufacture in the unopened container. Once opened, discard after 7 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Keppra film-coated tablets: Store below 25°C.

Keppra oral solution: Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Keppra film-coated tablets are blister packed and available in strengths of 250 mg, 500 mg, 750 mg* and 1000 mg levetiracetam.

250 mg: Available in blister packs containing 60 tablets.

500 mg: Available in blister packs containing 10*, 60 and 100* tablets.

750 mg:* Available in blister packs containing 60* tablets.

1000 mg: Available in blister packs containing 10*, 60 and 100* tablets.

**not currently distributed in Australia.*

Keppra oral solution is packed in 300 mL amber bottles with a child resistant closure and is available as 100 mg/mL strength. The pack also contains a 10 mL oral syringe with a graduation every 0.25 mL (25 mg) and an adaptor for the syringe.

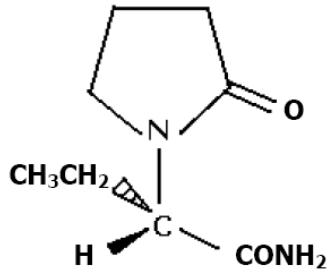
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical name: (S)-α-ethyl-2-oxo-1-pyrrolidineacetamide.
Molecular formula: $C_8H_{14}N_2O_2$.

Chemical structure



CAS number
102767-28-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

UCB Pharma
A division of UCB Australia Pty Ltd
250 Camberwell Road
Camberwell VIC 3124, Australia

9 DATE OF FIRST APPROVAL

7 September 2006

10 DATE OF REVISION

11 August 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8.0	Address Update

KEPPRA is a registered trademark of UCB Biopharma SPRL