

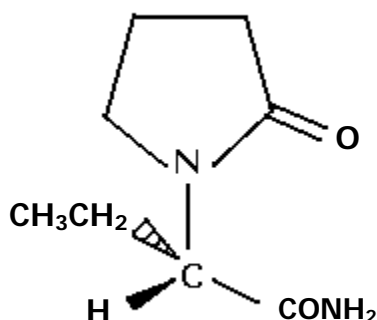
Data Sheet

Keppra (levetiracetam)

250mg, 500mg, 1000mg film-coated tablets

NAME OF THE DRUG

Keppra[®] film-coated tablet contains the active substance, levetiracetam; a pure enantiomer, with chemical name (S)- α -ethyl-2-oxo-1-pyrrolidine acetamide, formula C₈H₁₄N₂O₂, CAS-102767-28-2 and structure indicated below:



DESCRIPTION

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

PHARMACOLOGY

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 anti-epileptic 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 Ca²⁺ levels by partial inhibition of N-type Ca²⁺ currents and by reducing the release of Ca²⁺ 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 anti-seizure 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.

Pharmacokinetics

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

This pharmacokinetic profile was also confirmed with twice daily dosing of 1500 mg via intravenous infusion for 4 days.

There is no evidence for any relevant gender, race or circadian variability. The pharmacokinetic profile is comparable in adult healthy volunteers and adult patients with epilepsy.

A significant correlation between saliva and plasma concentrations has been shown in adults and children (ratio of saliva/plasma concentrations ranged from 1 to 1.6 for the oral tablets and after 4 hours post-dose for an oral solution formulation).

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 µg/mL and 43 µg/mL following a single 1000mg dose and repeated 1000mg 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 0.7L/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 culture, levetiracetam had little or no effect on ethinylestradiol conjugation or CYP1A1/2. Levetiracetam caused mild induction of CYP2B6 and CYP3A4 at high concentrations (680 µg/mL), however at concentrations approximating to the C_{max} following repeated 1500 mg twice daily dose, the effects were not considered to be biologically relevant. Therefore the interaction of Keppra with other substances, or *vice versa*, is unlikely.

Elimination

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 (refer DOSAGE AND ADMINISTRATION).

Children (4 to 12 years of age)

Following single dose administration (20mg/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 60mg/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 1.1mL/min/kg.

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

Following single dose administration (20mg/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 hours) than for adults (7.2 hours) and apparent clearance was faster (1.5mL/min/kg) than for adults (0.96mL/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 (refer DOSAGE AND ADMINISTRATION).

In anuric end-stage renal disease adult subjects the half-life was approximately 25 and 3.1 hours during inter- and intra-dialytic 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 (refer DOSAGE AND ADMINISTRATION).

CLINICAL TRIALS

Effectiveness in Partial Onset Seizures in Adult Patients with Epilepsy. The effectiveness of Keppra 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, 1000mg, 2000mg or 3000mg/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.

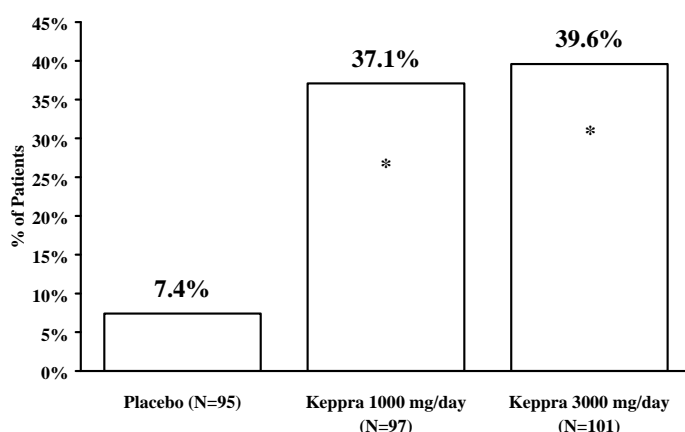
Study 1: Study 1 was a double-blind, placebo-controlled, parallel-group study conducted at 41 sites in the United States comparing Keppra 1000mg/day (N=97), Keppra 3000mg/day (N=101) and placebo (N=95) given in equally divided doses twice daily. After a prospective baseline period of 12 weeks, patients 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 $\geq 50\%$ reduction from baseline in partial onset seizure frequency). The results of the analysis of Study 1 are displayed in Table 1.

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

	Placebo (N=95)	Keppra 1000mg/day (N=97)	Keppra 3000mg/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 $\geq 50\%$ 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 ($\geq 50\%$ 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 1000mg/day (N=106), Keppra 2000mg/day (N=105) and placebo (N=111) given in equally divided doses twice daily.

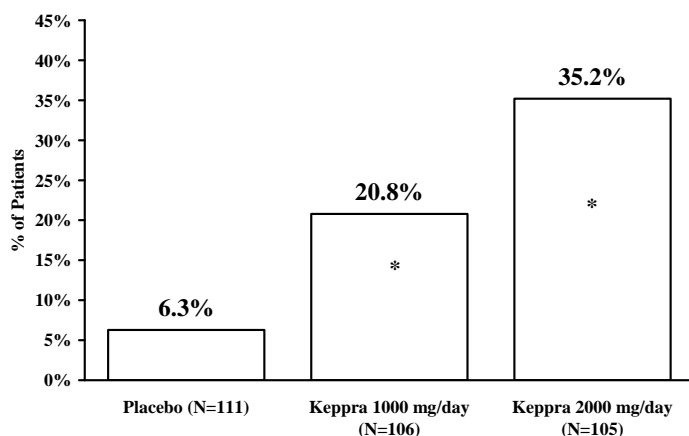
The first period of the study (Period A) was designed to be analysed as a parallel-group study. After a prospective baseline period of up to 12 weeks, patients were randomised to one of the three treatment groups described above. The 16-week treatment period consisted of the 4-week titration period followed 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 $\geq 50\%$ reduction from baseline in partial onset seizure frequency). The results of the analysis of Period A are displayed in Table 2.

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

	Placebo (N=111)	Keppra 1000mg/day (N=106)	Keppra 2000mg/day (N=105)
Percent reduction in partial seizure frequency over placebo	-	17.1% $P \leq 0.001$	21.4% $P \leq 0.001$

The percentage of patients (y-axis) who achieved $\geq 50\%$ 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 ($\geq 50\%$ reduction from baseline) in Study 2 – Period A.



* $P < 0.001$ versus placebo

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

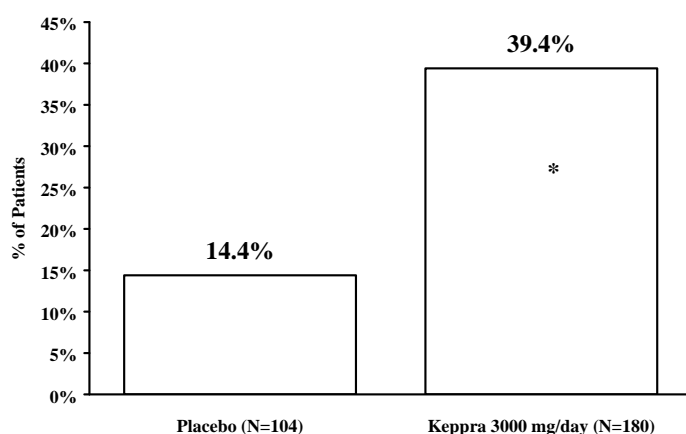
Study 3: Study 3 was a double-blind, placebo-controlled, parallel-group study conducted at 47 centres in Europe comparing Keppra 3000mg/day (N=180) and placebo (N=104) in patients with refractory partial onset seizures, with or without secondary generalisation, receiving only one concomitant AED. Study 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 $\geq 50\%$ reduction from baseline in partial onset seizure frequency). Table 3 displays the results of the analysis of Study 3.

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

	Placebo (N=104)	Keppra 3000mg/day (N=180)
Percent reduction in partial seizure frequency over placebo	-	23.0% $P < 0.001$

The percentage of patients (y-axis) who achieved $\geq 50\%$ 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 ($\geq 50\%$ 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, 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 Keppra or placebo. The population included 198 patients (Keppra 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 20mg/kg/day in two divided doses. During the treatment period, Keppra doses were adjusted in 20mg/kg/day increments, at 2-week intervals to the target dose of 60mg/kg/day (or 40mg/kg/day as a maximum tolerated dose).

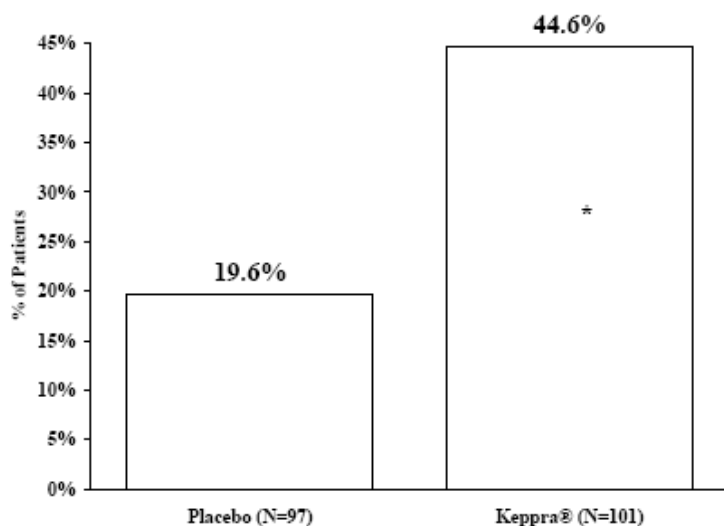
The primary measure of effectiveness was a between group comparison of the percent reduction in weekly partial seizure frequency relative to placebo over the entire 14-week randomized treatment period (titration + evaluation period). Secondary outcome variables included the responder rate (incidence of patients with $\geq 50\%$ reduction from baseline in partial onset seizure frequency per week). Table 4 displays the results of this study.

Table 4: 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 $\geq 50\%$ 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 ($\geq 50\%$ Reduction From Baseline)



* $P=0.0002$ versus placebo.

INDICATIONS

Keppra is indicated in epileptic patients aged 6 years and older, as add-on therapy, in the treatment of partial onset seizures with or without secondary generalisation.

CONTRAINDICATIONS

Hypersensitivity to any component of this product (refer to PRESENTATION).

PRECAUTIONS

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

An Analysis of reports of suicidality (suicidal behaviour or ideation) from placebo controlled clinical studies of eleven medicines used to treat epilepsy as well as psychiatric disorders, and other conditions revealed that patients receiving antiepileptic drugs had approximately twice the risk of suicidal behaviour or ideation (0.43%) compared to patients receiving placebo (0.22%). The increased risk of suicidal behaviour and suicidal ideation was observed as early as one week after starting the anti-epileptic medicine and continued through 24 weeks. The results were generally consistent among the eleven medicines. Patients who were treated for epilepsy, psychiatric disorders, and other conditions were all at increased risk of suicidality when compared to placebo, and there did not appear to be a specific demographic subgroup of patients to which the increased risk could be attributed. The relative risk of suicidality was higher in the patients with epilepsy compared to patients who were given one of the medicines in the class for psychiatric or other conditions.

All Patients who are currently taking or starting on any anti-epileptic drug should be closely monitored for notable changes in behaviour that could indicate the emergence or worsening of suicidal thoughts or behaviour or depression.

Health Care Professionals should inform patients, their families, and caregivers of the potential for an increase in the risk of suicidality. Prescribers should advise patients to seek medical advice immediately if they develop any symptoms suggestive of suicidality.

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.

To date, there are no data to support the use of levetiracetam in patients less than 4 years of age. No data on the interaction of levetiracetam with alcohol are available.

Impaired renal function

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 (refer DOSAGE AND ADMINISTRATION).

Carcinogenesis

Rats were dosed with levetiracetam in the diet for 104 weeks at doses of 50, 300 and 1800 mg/kg/day. The highest dose corresponds to 6 times the maximum recommended daily human dose (MRHD) of 3000 mg on a mg/m² basis and it also provided systemic exposure (AUC) approximately 6 times that achieved in humans receiving the MRHD. There was no evidence of carcinogenicity. Two studies have been conducted in mice. In one study, mice received levetiracetam in the diet for 80 weeks at doses of 60, 240 and 960 mg/kg/day (high dose is equivalent to 2 times the MRHD on a mg/m² or exposure basis). In a second study, mice received levetiracetam by oral gavage for 2 years at dose levels of 1000, 2000 and 4000 mg/kg/day. Due to poor survival at the highest dose of 4000 mg/kg/day in this study, the high dose was reduced to 3000 mg/kg/day (equivalent to 12 times the MRHD). Neither study showed evidence of carcinogenicity.

Genotoxicity

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

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 1800mg/kg/day (corresponding to approximately 6 times the maximal recommended clinical dose on a mg/m² 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.

In reproductive toxicity studies in the rat, levetiracetam induced developmental toxicity (increase in skeletal variations/minor anomalies, retarded growth, increased pup mortality) at exposure levels similar to or greater than the human exposure. In the rabbit foetal effects (embryonic death, increased skeletal anomalies and increased malformations) were observed in the presence of maternal toxicity. The systemic exposure at the observed no effect level in the rabbit was about 4 to 5 times the human exposure.

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 1800mg/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 pre-pregnancy 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 (5mg) should be commenced four weeks prior to and continue for twelve weeks after conception;
- specialist prenatal diagnosis including detailed mid-trimester ultrasound should be offered.

To date, insufficient clinical data on exposed pregnancies are available. 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. There have been reports of decreased levetiracetam concentration during pregnancy. This decrease is more pronounced during the third trimester (up to 60 % of baseline concentration before pregnancy).

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.

Interactions with other drugs

In vitro, levetiracetam and its major metabolite (ucb L057) have been shown not to inhibit the major human liver cytochrome P450 isoforms, glucuronyl transferase, 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 a probenecid was not studied and the effect of levetiracetam on other actively secreted drugs, e.g. NSAIDs, sulphonamides, and methotrexate is unknown.

Pre-marketing 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 60mg/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, lamotrigine and topiramate. 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 (ethinyl-estradiol 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.

Effect on ability to drive or operate machinery

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.

ADVERSE REACTIONS

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.

Very common adverse events ($\geq 10\%$)

The very common adverse events ($\geq 10\%$) 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

Table 5: 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 ($0.03 \times 10^6/\text{mm}^2$), mean hemoglobin (0.9g/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 ($\geq 1\%$, $< 10\%$):

Table 6: 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
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

Body System / Adverse Event	Keppra group (N=672) %	Placebo group (N=351) %
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%).

Table 7: 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		
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

Body System / Adverse Event	Keppra group (N=101) %	Placebo group (N=97) %
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, pruritis
- Blood and lymphatic system disorders: Common: thrombocytopenia
- Eye disorders: Common: vision blurred

- Musculoskeletal and connective tissue disorders: Common: myalgia
- Psychiatric disorders: Common: irritability, mood swings, personality disorder

Postmarketing Experience

In post-marketing 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 post-marketing 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, leucopenia and neutropenia.
- Psychiatric disorders: abnormal behaviour, aggression, anger, panic attack, confusion, hallucination, psychotic disorder, suicide, suicide attempt and suicidal ideation.
- Nervous system disorders: choreoathetosis, dyskinesia, lethargy
- Skin and subcutaneous tissue disorders: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme and alopecia; in several alopecia cases, recovery was observed when Keppra was discontinued.
- Musculoskeletal and connective tissue disorders: muscular weakness
- Liver and biliary system disorders: hepatitis, hepatic failure and abnormal liver function test
- Metabolic and nutritional disorders: weight loss, pancreatitis

DOSAGE AND ADMINISTRATION

The film-coated tablets must be taken orally, swallowed with liquid and may be taken with or without food. The daily dose is administered in two equally divided doses.

Adults (>18 years of age) and adolescents (aged 12-17 years of age) of 50kg or more

As adjunctive therapy, the therapeutic dose is 500mg 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 1500mg twice daily. Dose changes can be made in 500mg twice daily increments or decrements every 2 to 4 weeks. The maximum recommended daily dose is 3000mg.

Elderly (65 years and older)

Adjustment of the dose is recommended in the elderly with compromised renal function (refer "Patients with renal impairment" below).

Children (aged 6 to 11 years of age) and adolescents (aged 12-17 years of age) of less than 50kg

The initial therapeutic dose is 10mg/kg twice daily. Refer to Table 8.

Depending on the clinical response and tolerance, the daily dose can be increased up to 60mg/kg daily (in two 30mg/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 50kg or greater is the same as in adults.

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

Table 8: Recommended dosing in children aged 6 years and older

Weight	Starting dose: 10mg/kg twice daily	Maximum dose: 30mg/kg twice daily
25 kg	250mg twice daily	750mg twice daily
From 50 kg ⁽¹⁾	500mg twice daily	1500mg twice daily

⁽¹⁾ Dosage in children and adolescents 50kg or more is the same as in adults.

Infants and children less than 6 years of age

Keppra tablets are not recommended for use in children under 6 years of age.

Patients with renal impairment

The Keppra daily dose must be individualised according to renal function. For adult patients refer to Table 9 and adjust the dose as indicated.

Table 9: 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 750mg loading dose is recommended on the first day of treatment with levetiracetam.

(2) Following dialysis, a 250 to 500mg supplemental dose is recommended.

To use this dosing table an estimate of the patient's creatinine clearance (CL_{cr}) in mL/min is needed. The CL_{cr} in mL/min may be estimated from serum creatinine (mg/dL) determination using the following formula:

$$CL_{cr} = \frac{[140 - \text{age}(\text{years})] \times \text{weight}(\text{kg})}{72 \times \text{serum creatinine}(\text{mg/dL})} \quad (\times 0.85 \text{ for women})$$

The CL_{cr} is adjusted for body surface area (BSA) as follows:

$$CL_{cr}(\text{mL/min/1.73m}^2) = \frac{CL_{cr}(\text{mL/min})}{BSA \text{ subject}(\text{m}^2)} \times 1.73$$

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/1.73m².

OVERDOSE

The highest known dose of Keppra received in the clinical development program was 6000mg/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. After an acute overdose, the stomach may be emptied by gastric lavage or by induction of emesis. 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).

PRESENTATION

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

250 mg Blue, oblong, scored film-coated tablet debossed with the code ucb and 250 on one side. The coating consists of: polyvinyl alcohol, titanium dioxide, macrogol 3350, talc and indigo carmine CI73015. Available in a blister pack containing 60 tablets.

500 mg Yellow, oblong, scored film-coated tablet debossed with the code ucb and 500 on one side. The coating consists of: polyvinyl alcohol, titanium dioxide, macrogol 3350, talc and iron oxide yellow CI77492. Available in blister packs containing 10, 60 and 100 tablets.

1000 mg White, oblong, scored film-coated tablet debossed with the code ucb and 1000 on one side. The coating consists of: polyvinyl alcohol, titanium dioxide, macrogol 3350 and talc. Available in blister packs containing 10, 60 and 100 tablets.

Each tablet contains the following excipients: Croscarmellose sodium, macrogol 6000, silica-colloidal anhydrous, magnesium stearate

Keppra film-coated tablets are stable for 30 months from date of manufacture when stored below 25°C.

NAME AND ADDRESS OF THE SPONSOR

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Keppra is a registered trademark of UCB Pharma, SA.

POISON SCHEDULE

S4: Keppra is a prescription only medication.

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