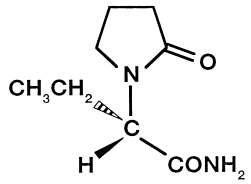
KEPPRA™ (levetiracetam) **Rx only**
250 mg, 500 mg and 750 mg tablets

DESCRIPTION

Keppra™ (levetiracetam) is an antiepileptic drug available as 250 mg (blue), 500 mg (yellow) and 750 mg (orange) tablets for oral administration.

The chemical name of levetiracetam, a single enantiomer, is (-)-(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide, its molecular formula is $C_8H_{14}N_2O_2$ and its molecular weight is 170.21. Levetiracetam is chemically unrelated to existing antiepileptic drugs (AEDs). It has the following structural formula:



Levetiracetam is a white to off-white crystalline powder with a faint odor and a bitter taste. It is very soluble in water (104.0 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 tablets contain the labeled amount of levetiracetam. Inactive ingredients: colloidal silicon dioxide, corn starch, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol 4000, povidone, talc, titanium dioxide and coloring agents.

The individual tablets contain the following coloring agents:

250 mg tablets: FD&C Blue No. 2,
500 mg tablets: FD&C Blue No. 2 and yellow iron oxide,
750 mg tablets: FD&C Blue No. 2, FD&C Yellow No. 6 and red iron oxide.

CLINICAL PHARMACOLOGY

Mechanism Of Action

The precise mechanism(s) by which levetiracetam exerts its antiepileptic effect is unknown and does not appear to derive from any interaction with known mechanisms involved in inhibitory and excitatory neurotransmission. The antiepileptic activity of levetiracetam was assessed in a number of animal models of epileptic seizures. Levetiracetam did not inhibit single seizures induced by maximal stimulation with electrical current or different chemoconvulsants and showed only minimal activity in submaximal stimulation and in threshold tests. Protection was observed, however, against secondarily generalized activity from focal seizures induced by pilocarpine and kainic acid, two chemoconvulsants that induce seizures that mimic some features of

human complex partial seizures with secondary generalization. Levetiracetam also displayed inhibitory properties in the kindling model in rats, another model of human complex partial seizures, both during kindling development and in the fully kindled state. The predictive value of these animal models for specific types of human epilepsy is uncertain.

In vitro studies show that levetiracetam, up to 1700 μg/mL, did not result in significant ligand displacement at known receptor binding sites. Second messenger systems, ion channel proteins, glutamate receptor-mediated neurotransmission, muscimol-induced chloride flux and gamma-aminobutyric acid-transaminase and glutamate decarboxylase activities were unaffected by levetiracetam. Benzodiazepine receptor antagonists had no effect on levetiracetam's protection against seizures. In contrast, a stereoselective binding site for the drug has been demonstrated to exist exclusively in synaptic plasma membranes in the CNS, and not in peripheral tissue.

In vitro and *in vivo* recordings of epileptiform activity from the hippocampus have shown that levetiracetam inhibits burst firing without affecting normal neuronal excitability, suggesting that levetiracetam may selectively prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity.

Pharmacokinetics

The pharmacokinetics of levetiracetam have been studied in healthy adult subjects, adults and pediatric patients with epilepsy, elderly subjects and subjects with renal and hepatic impairment.

Overview

Levetiracetam is rapidly and almost completely absorbed after oral administration. The pharmacokinetics are linear and time-invariant, with low intra- and inter-subject variability. The extent of bioavailability of levetiracetam is not affected by food. Levetiracetam is not protein-bound (<10% bound) and its volume of distribution is close to the volume of intracellular and extracellular water. Sixty-six percent (66%) of the dose is renally excreted unchanged. The major metabolic pathway of levetiracetam (24% of dose) is an enzymatic hydrolysis of the acetamide group. It is not liver cytochrome P450 dependent. The metabolites have no known pharmacological activity and are renally excreted. Plasma half-life of levetiracetam across studies is approximately 6-8 hours. It is increased in the elderly (primarily due to impaired renal clearance) and in subjects with renal impairment.

Absorption and Distribution

Absorption of levetiracetam is rapid, with peak plasma concentrations occurring in about an hour following oral administration in fasted subjects. The oral bioavailability of levetiracetam tablets is 100%. Food does not affect the extent of absorption of levetiracetam but it decreases C_{max} by 20% and delays T_{max} by 1.5 hours. The

pharmacokinetics of levetiracetam are linear over the dose range of 500-5000 mg. Steady state is achieved after 2 days of multiple twice daily dosing. Levetiracetam and its major metabolite are less than 10% bound to plasma proteins; clinically significant interactions with other drugs through competition for protein binding sites are therefore unlikely.

Metabolism

Levetiracetam is not extensively metabolized in humans. The major metabolic pathway is the enzymatic hydrolysis of the acetamide group, which produces the carboxylic acid metabolite, ucb L057 (24%) and is not dependent on any liver cytochrome P450 isoenzymes. The major metabolite is inactive in animal seizure models. Two minor metabolites were identified as the product of hydroxylation of the 2-oxo-pyrrolidine ring (2% of dose) and opening of the 2-oxo-pyrrolidine ring in position 5 (1% of dose). There is no enantiomeric interconversion of levetiracetam or its major metabolite.

Elimination

Levetiracetam plasma half-life in adults is 7 ± 1 hour and is unaffected by either dose or repeated administration. Levetiracetam is eliminated from the systemic circulation by renal excretion as unchanged drug which represents 66% of administered dose. The total body clearance is 0.96 mL/min/kg and the renal clearance is 0.6 mL/min/kg. The mechanism of excretion is glomerular filtration with subsequent partial tubular reabsorption. The metabolite ucb L057 is excreted by glomerular filtration and active tubular secretion with a renal clearance of 4 mL/min/kg. Levetiracetam elimination is correlated to creatinine clearance. Levetiracetam clearance is reduced in patients with impaired renal function, (see Special Populations, Renal Impairment and DOSAGE AND ADMINISTRATION, Patients with Impaired Renal Function).

Pharmacokinetic Interactions

In vitro data on metabolic interactions indicate that levetiracetam is unlikely to produce, or be subject to, pharmacokinetic interactions. Levetiracetam and its major metabolite, at concentrations well above C_{max} levels achieved within the therapeutic dose range, are neither inhibitors of, nor high affinity substrates for human liver cytochrome P450 isoforms, epoxide hydrolase or UDP-glucuronidation enzymes. In addition, levetiracetam does not affect the in vitro glucuronidation of valproic acid.

Potential pharmacokinetic interactions were assessed in clinical pharmacokinetic studies (phenytoin, warfarin, digoxin, oral contraceptives) and through pharmacokinetic screening in the placebo-controlled clinical studies in epilepsy patients (see PRECAUTIONS, Drug Interactions).

Special Populations

Elderly

Pharmacokinetics of levetiracetam were evaluated in 16 elderly subjects (age 61-88 years) with creatinine clearance ranging from 30 to 74 mL/min. Following oral administration of twice daily dosing for 10 days, total body clearance decreased by 38% and the half-life was 2.5 hours longer in the elderly compared to healthy adults. This is most likely due to the decrease in renal function in these subjects.

Pediatric Patients

Pharmacokinetics of levetiracetam were evaluated in 24 pediatric patients (age 6-12 years) after single dose (20 mg/kg). The apparent clearance of levetiracetam was approximately 40% higher than in adults.

Gender

Levetiracetam C_{max} and AUC were 20% higher in women (N=11) compared to men (N=12). However, clearances adjusted for body weight were comparable.

Race

Formal pharmacokinetic studies of the effects of race have not been conducted. Cross study comparisons involving Caucasians (N=12) and Asians (N=12), however, show that pharmacokinetics of levetiracetam were comparable between the two races. Because levetiracetam is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

Renal Impairment

The disposition of levetiracetam was studied in subjects with varying degrees of renal function. Total body clearance of levetiracetam is reduced in patients with impaired renal function by 40% in the mild group (CLcr = 50-80 mL/min), 50% in the moderate group (CLcr = 30-50 mL/min), and 60% in the severe renal impairment group (CLcr <30 mL/min). Clearance of levetiracetam is correlated with creatinine clearance.

In anuric (end stage renal disease) patients, the total body clearance decreased 70% compared to normal subjects (CLcr >80mL/min). Approximately 50% of the pool of levetiracetam in the body is removed during a standard 4-hour hemodialysis procedure.

Dosage should be reduced in patients with impaired renal function receiving levetiracetam, and supplemental doses should be given to patients after dialysis (see PRECAUTIONS, DOSAGE AND ADMINISTRATION, Patients with Impaired Renal Function).

Hepatic Impairment

In subjects with mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment, the pharmacokinetics of levetiracetam were unchanged. In patients with severe hepatic impairment (Child-Pugh C), total body clearance was 50% that of normal subjects, but

decreased renal clearance accounted for most of the decrease. No dose adjustment is needed for patients with hepatic impairment.

CLINICAL STUDIES

Effectiveness In Partial Onset Seizures

The effectiveness of Keppra as adjunctive therapy (added to other antiepileptic drugs) in adults was established in three multicenter, randomized, double-blind, placebo-controlled clinical studies in patients who had refractory partial onset seizures with or without secondary generalization. In these studies, 904 patients were randomized 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. At the time of the study, patients were taking a stable dose regimen of at least one and could take a maximum of 2 AEDs. During the baseline period, patients had to have experienced at least 4 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 randomized 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 randomized treatment period (titration + evaluation period). Secondary outcome variables included the responder rate (incidence of patients with ≥50% reduction from baseline in partial onset seizure frequency). The results of the analysis of Study 1 are displayed in Table 1.

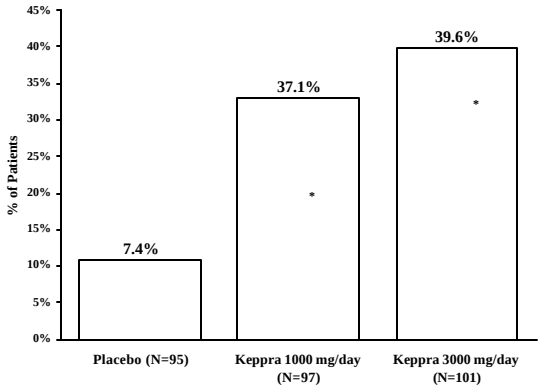
Table 1. Reduction In Weekly Frequency Of Partial Onset Seizures In Study 1

	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%*	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 randomized 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 centers 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 analyzed as a parallel-group study. After a prospective baseline period of up to 12 weeks, patients were randomized 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 randomized treatment period (titration + evaluation period). Secondary outcome variables included the responder rate (incidence of patients with ≥50% reduction from baseline in partial onset seizure frequency). The results of the analysis of Period A are displayed in Table 2.

Table 2. Reduction In Weekly Frequency Of Partial Onset Seizures In Study 2: Period A

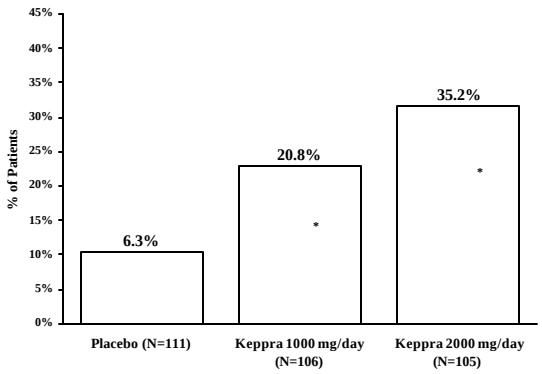
	Placebo (N=111)	Keppra 1000 mg/day (N=106)	Keppra 2000 mg/day (N=105)
Percent reduction in partial seizure frequency over placebo	–	17.1%*	21.4%*

* 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 randomized 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 cross-over yielded similar results.

Study 3

Study 3 was a double-blind, placebo-controlled, parallel-group study conducted at 47 centers in Europe comparing Keppra 3000 mg/day (N=180) and placebo (N=104) in patients with refractory partial onset seizures, with or without secondary generalization, receiving only one concomitant AED. Study drug was given in two divided doses. After a prospective baseline period of 12 weeks, patients were randomized 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 randomized treatment period (titration + evaluation period). Secondary outcome variables included the responder rate (incidence of patients with ≥50% reduction from baseline in partial onset seizure frequency). Table 3 displays the results of the analysis of Study 3.

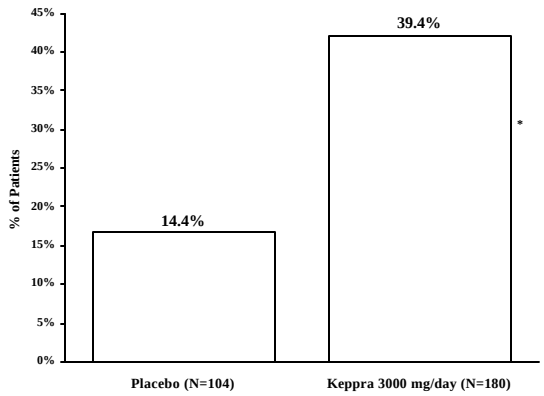
Table 3. Reduction In Weekly Frequency Of Partial Onset Seizures In Study 3

	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 randomized 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<0.001versus placebo

INDICATIONS AND USAGE

Keppra (levetiracetam) is indicated as adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to levetiracetam or any of the inactive ingredients in Keppra tablets.

WARNINGS

Neuropsychiatric Adverse Events

Keppra use is associated with the occurrence of central nervous system adverse events that can be classified into the following categories: 1) somnolence and fatigue, 2) coordination difficulties, and 3) behavioral abnormalities.

In controlled trials of patients with epilepsy, 14.8% of Keppra treated patients reported somnolence, compared to 8.4% of placebo patients. There was no clear dose response up to 3000 mg/day. In a study where there was no titration, about 45% of patients receiving 4000 mg/day reported somnolence. The somnolence was considered serious in 0.3% of the treated patients, compared to 0% in the placebo group. About 3% of Keppra treated

patients discontinued treatment due to somnolence, compared to 0.7% of placebo patients. In 1.4% of treated patients and in 0.9% of placebo patients the dose was reduced, while 0.3% of the treated patients were hospitalized due to somnolence.

In controlled trials of patients with epilepsy, 14.7% of treated patients reported asthenia, compared to 9.1% of placebo patients. Treatment was discontinued in 0.8% of treated patients as compared to 0.5% of placebo patients. In 0.5% of treated patients and in 0.2% of placebo patients the dose was reduced.

A total of 3.4% of Keppra treated patients experienced coordination difficulties, (reported as either ataxia, abnormal gait, or incoordination) compared to 1.6% of placebo patients. A total of 0.4% of patients in controlled trials discontinued Keppra treatment due to ataxia, compared to 0% of placebo patients. In 0.7% of treated patients and in 0.2% of placebo patients the dose was reduced due to coordination difficulties, while one of the treated patients was hospitalized due to worsening of pre-existing ataxia.

Somnolence, asthenia and coordination difficulties occurred most frequently within the first four weeks of treatment.

In controlled trials of patients with epilepsy, 5 (0.7%) of Keppra treated patients experienced psychotic symptoms compared to 1 (0.2%) placebo patient. Two (0.3%) Keppra treated patients were hospitalized and their treatment was discontinued. Both events, reported as psychosis, developed within the first week of treatment and resolved within one to two weeks following treatment discontinuation. Two other events, reported as hallucinations, occurred after 1-5 months and resolved within 2-7 days while the patients remained on treatment. In one patient experiencing psychotic depression occurring with in a month, symptoms resolved within 45 days while the patient continued treatment. A total of 13.3% of Keppra patients experienced other behavioral symptoms (reported as agitation, hostility, anxiety, apathy, emotional lability, depersonalization, depression, etc.) compared to 6.2% of placebo patients. Approximately half of these patients reported these events within the first four weeks. A total of 1.7% of treated patients discontinued treatment due to these events, compared to 0.2% of placebo patients. The treatment dose was reduced in 0.8% of treated patients and in 0.5% of placebo patients. A total of 0.8% of treated patients had a serious behavioral event (compared to 0.2% of placebo patients) and were hospitalized.

In addition, 4 (0.5%) of treated patients attempted suicide compared to 0% of placebo patients. One of these patients successfully committed suicide. In the other 3 patients, the events did not lead to discontinuation or dose reduction. The events occurred after patients had been treated for between four weeks and six months.

Withdrawal Seizures

Antiepileptic drugs, including Keppra, should be withdrawn gradually to minimize the potential of increased seizure frequency.

PRECAUTIONS

Hematologic Abnormalities

Minor, but statistically significant, decreases compared to placebo in total mean RBC count (0.03 x $10^6/mm^2$), mean hemoglobin (0.09 g/dL), and mean hematocrit (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 x 10^9/L) decreased WBC, and 2.4% of treated and 1.4% of placebo patients had at least one possibly significant ($\leq$ 1.0 x 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.

Hepatic Abnormalities

There were no meaningful changes in mean liver function tests (LFT) in controlled trials; lesser LFT abnormalities were similar in drug and placebo treated patients in controlled trials (1.4%). No patients were discontinued from controlled trials for LFT abnormalities except for 1 (0.07%) epilepsy patient receiving open treatment.

Information For Patients

Patients should be instructed to take Keppra only as prescribed.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised that Keppra may cause dizziness and somnolence. Accordingly, patients should be advised not to drive or operate machinery or engage in other hazardous activities until they have gained sufficient experience on Keppra to gauge whether it adversely affects their performance of these activities.

Laboratory Tests

Although most laboratory tests are not systematically altered with Keppra treatment, there have been relatively infrequent abnormalities seen in hematologic parameters and liver function tests.

Use in Patients with Impaired Renal Function

Caution should be taken in dosing patients with moderate and severe renal impairment and patients undergoing hemodialysis. Dosage should be reduced in patients with impaired renal function receiving Keppra and supplemental doses should be given to

patients after dialysis (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION, Patients with Impaired Renal Function).

Drug Interactions

In vitro data on metabolic interactions indicate that Keppra is unlikely to produce, or be subject to, pharmacokinetic interactions. Levetiracetam and its major metabolite, at concentrations well above Cmax levels achieved within the therapeutic dose range, are neither inhibitors of nor high affinity substrates for human liver cytochrome P450 isoforms, epoxide hydrolase or UDP-glucuronidation enzymes. In addition, levetiracetam does not affect the in vitro glucuronidation of valproic acid.

Levetiracetam circulates largely unbound (<10% bound) to plasma proteins; clinically significant interactions with other drugs through competition for protein binding sites are therefore unlikely.

Potential pharmacokinetic interactions were assessed in clinical pharmacokinetic studies (phenytoin, warfarin, digoxin, oral contraceptive) and through pharmacokinetic screening in the placebo-controlled clinical studies in epilepsy patients.

Drug-Drug Interactions between Keppra and Existing Antiepileptic Drugs (AEDs)

Potential drug interactions between Keppra and existing AEDs (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) were assessed by evaluating the serum concentrations of levetiracetam and these AEDs during placebo-controlled clinical studies. These data indicate that levetiracetam does not influence the plasma concentration of existing AEDs and that these AEDs do not influence the pharmacokinetics of levetiracetam.

Other Drug Interactions

Oral Contraceptives

Keppra (500 mg twice daily) did not influence the pharmacokinetics of an oral contraceptive containing 0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel, or of the luteinizing hormone and progesterone levels, indicating that impairment of contraceptive efficacy is unlikely. Coadministration of this oral contraceptive did not influence the pharmacokinetics of levetiracetam.

Digoxin

Keppra (1000 mg twice daily) did not influence the pharmacokinetics and pharmacodynamics (ECG) of digoxin given as a 0.25 mg dose every day. Coadministration of digoxin did not influence the pharmacokinetics of levetiracetam.

Warfarin

Keppra (1000 mg twice daily) did not influence the pharmacokinetics of R and S warfarin. Prothrombin time was not affected by levetiracetam. Coadministration of warfarin did not affect the pharmacokinetics of levetiracetam.

Probenecid

Probenecid, a renal tubular secretion blocking agent, administered at a dose of 500 mg four times a day, did not change the pharmacokinetics of levetiracetam 1000 mg twice daily. C^{ss}_{max} of the metabolite, ucb L057, was approximately doubled in the presence of probenecid while the fraction of drug excreted unchanged in the urine remained the same. Renal clearance of ucb L057 in the presence of probenecid decreased 60%, probably related to competitive inhibition of tubular secretion of ucb L057.
The effect of Keppra on probenecid was not studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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/m^2 basis and it also provided systemic exposure (AUC) approximately 6 times that achieved in humans receiving the MRHD. There was no evidence of carcinogenicity. A study was conducted in which 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/m^2 or exposure basis). Although no evidence for carcinogenicity was seen, the potential for a carcinogenic response has not been fully evaluated in that species because adequate doses have not been studied.

Mutagenesis

Levetiracetam was not mutagenic in the Ames test or in mammalian cells in vitro in the Chinese hamster ovary/HGPRT locus assay. It was not clastogenic in an in vitro analysis of metaphase chromosomes obtained from Chinese hamster ovary cells or in an in vivo mouse micronucleus assay. The hydrolysis product and major human metabolite of levetiracetam (L057) was not mutagenic in the Ames test or the in vitro mouse lymphoma assay.

Impairment Of Fertility

No adverse effects on male or female fertility or reproductive performance were observed in rats at doses up to 1800 mg/kg/day (approximately 6 times the maximum recommended human dose on a mg/m^2 or exposure basis).

Pregnancy

Pregnancy Category C

In animal studies, levetiracetam produced evidence of developmental toxicity at doses similar to or greater than human therapeutic doses.

Administration to female rats throughout pregnancy and lactation was associated with increased incidences of minor fetal skeletal abnormalities and retarded offspring growth pre- and/or postnatally at doses ≥ 350 mg/kg/day (approximately equivalent to the maximum recommended human dose of 3000 mg [MRHD] on a mg/m^2 basis) and with increased pup mortality and offspring behavioral alterations at a dose of 1800 mg/kg/day (6 times the MRHD on a mg/m^2 basis). The developmental no effect dose was 70 mg/kg/day (0.2 times the MRHD on a mg/m^2 basis). There was no overt maternal toxicity at the doses used in this study.

Treatment of pregnant rabbits during the period of organogenesis resulted in increased embryofetal mortality and increased incidences of minor fetal skeletal abnormalities at doses ≥ 600 mg/kg/day (approximately 4 times MRHD on a mg/m^2 basis) and in decreased fetal weights and increased incidences of fetal malformations at a dose of 1800 mg/kg/day (12 times the MRHD on a mg/m^2 basis). The developmental no effect dose was 200 mg/kg/day (1.3 times the MRHD on a mg/m^2 basis). Maternal toxicity was also observed at 1800 mg/kg/day.

When pregnant rats were treated during the period of organogenesis, fetal weights were decreased and the incidence of fetal skeletal variations was increased at a dose of 3600 mg/kg/day (12 times the MRHD). 1200 mg/kg/day (4 times the MRHD) was a developmental no effect dose. There was no evidence of maternal toxicity in this study.

Treatment of rats during the last third of gestation and throughout lactation produced no adverse developmental or maternal effects at doses of up to 1800 mg/kg/day (6 times the MRHD on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. Keppra should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy Exposure Registry

To facilitate monitoring fetal outcomes of pregnant women exposed to Keppra physicians are encouraged to register patients, before fetal outcome is known (e.g., ultrasound, results of amniocentesis, etc.), in the Antiepileptic Drug Pregnancy Registry by calling (888) 233-2334 (toll free).

Labor And Delivery

The effect of Keppra on labor and delivery in humans is unknown.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Keppra is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in patients below the age of 16 have not been established.

Geriatric Use

Of the total number of subjects in clinical studies of levetiracetam, 347 were 65 and over. No overall differences in safety were observed between these subjects and younger subjects. There were insufficient numbers of elderly subjects in controlled trials of epilepsy to adequately assess the effectiveness of Keppra in these patients.

A study in 16 elderly subjects (age 61-88 years) with oral administration of single dose and multiple twice-daily doses for 10 days showed no pharmacokinetic differences related to age alone.

Levetiracetam is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Use In Patients With Impaired Renal Function

Clearance of levetiracetam is decreased in patients with renal impairment and is correlated with creatinine clearance. The dosage should be reduced in patients with impaired renal function receiving Keppra and supplemental doses should be given to patients after dialysis (see DOSAGE AND ADMINISTRATION, Patients with Impaired Renal Function).

ADVERSE REACTIONS

In well-controlled clinical studies, the most frequently reported adverse events associated with the use of Keppra in combination with other AEDs, not seen at an equivalent frequency among placebo-treated patients, were somnolence, asthenia, infection and dizziness.

Table 4 lists treatment-emergent adverse events that occurred in at least 1% of patients with epilepsy treated with Keppra participating in placebo-controlled studies and were numerically more common in patients treated with Keppra than placebo. In these studies,

either Keppra or placebo was added to concurrent AED therapy. Adverse events were usually mild to moderate in intensity.

The prescriber should be aware that these figures, obtained when Keppra was added to concurrent AED therapy, cannot be used to predict the frequency of adverse experiences in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

Table 4: Incidence (%) Of Treatment-Emergent Adverse Events In Placebo-Controlled, Add-On Studies by Body System. (Adverse Events Occurred In At Least 1% Of Keppra - Treated Patients And Occurred More Frequently Than Placebo-Treated Patients.)

Body System/ Adverse Event	Keppra **(N = 769) %**	**Placebo (N=439) %**
Body as a Whole		
Asthenia	15	9
Headache	14	13
Infection	13	8
Pain	7	6
Digestive System		
Anorexia	3	2
Nervous System		
Amnesia	2	1
Anxiety	2	1
Ataxia	3	1
Depression	4	2
Dizziness	9	4
Emotional Lability	2	0
Hostility	2	1
Nervousness	4	2
Paresthesia	2	1
Somnolence	15	8
Vertigo	3	1
Respiratory System		
Cough Increased	2	1
Pharyngitis	6	4
Rhinitis	4	3
Sinusitis	2	1
Special Senses		
Diplopia	2	1

Other events reported by 1% or more of patients treated with Keppra but as or more frequent in the placebo group were: abdominal pain, accidental injury, amblyopia, arthralgia, back pain, bronchitis, chest pain, confusion, constipation, convulsion, diarrhea, drug level increased, dyspepsia, ecchymosis, fever, flu syndrome, gastroenteritis,

gingivitis, grand mal convulsion, infection fungal, insomnia, nausea, otitis media, rash, thinking abnormal, tremor, urinary tract infection, vomiting and weight gain.

Time Course Of Onset Of Adverse Events

Of the most frequently reported adverse events, asthenia, somnolence and dizziness appeared to occur predominantly during the first four weeks of treatment with Keppra.

Discontinuation Or Dose Reduction In Well-Controlled Clinical Studies

In well-controlled clinical studies, 15.0% of patients receiving Keppra and 11.6% receiving placebo either discontinued or had a dose reduction as a result of an adverse event. The adverse events most commonly associated (>1%) with discontinuation or dose reduction in either treatment group are presented in Table 5.

Table 5: Adverse Events Most Commonly Associated With Discontinuation Or Dose Reduction In Placebo-Controlled Studies In Patients With Epilepsy

	Number (%)	
	Keppra (N= 769)	Placebo (N = 439)
Asthenia	10 (1.3%)	3 (0.7%)
Convulsion	23 (3.0%)	15 (3.4%)
Dizziness	11 (1.4%)	0
Somnolence	34 (4.4%)	7 (1.6%)
Rash	0	5 (1.1%)

Comparison Of Gender, Age And Race

The overall adverse experience profile of Keppra was similar between females and males. There are insufficient data to support a statement regarding the distribution of adverse experience reports by age and race.

DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of Keppra has not been evaluated in human studies.

OVERDOSAGE

Signs, Symptoms And Laboratory Findings Of Acute Overdosage In Humans

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.

Treatment Or Management Of Overdose

There is no specific antidote for overdose with Keppra. If indicated, elimination of unabsorbed drug should be attempted by emesis or gastric lavage; usual precautions should be observed to maintain airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of patient. A Certified Poison Control Center should be contacted for up to date information on the management of overdose with Keppra.

Hemodialysis

Standard hemodialysis procedures result in significant clearance of levetiracetam (approximately 50% in 4 hours) and should be considered in cases of overdose. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

DOSAGE AND ADMINISTRATION

Keppra is indicated as adjunctive treatment of partial onset seizures in adults with epilepsy.

In clinical trials, daily doses of 1000 mg, 2000 mg, and 3000 mg, given as twice a day dosing, were shown to be effective. Although in some studies there was a tendency toward greater response with higher dose (see Clinical Studies) a consistent increase in response with increased dose has not been shown.

Treatment should be initiated with a daily dose of 1000 mg/day, given as twice daily dosing (500 mg BID). Additional dosing increments may be given (1000 mg/day additional every 2 weeks) to a maximum recommended daily dose of 3000 mg. Long term experience at doses greater than 3000 mg/day is relatively minimal, and there is no evidence that doses greater than 3000 mg/day confer additional benefit.

Keppra is given orally with or without food.

Patients With Impaired Renal Function

Keppra dosing must be individualized according to the patient's renal function status. Recommended doses and adjustment for dose are shown in the Table below. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in mL/min is needed. CLcr in mL/min may be estimated from serum creatinine (mg/dL) determination using the following formula:

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

Dosing Adjustment Regimen for Patients with Impaired Renal Function

Group	Creatinine Clearance (mL/min)	Dosage (mg)	Frequency
Normal	>80	500 to 1,500	Every 12 h
Mild	50-80	500 to 1,000	Every 12 h
Moderate	30-50	250 to 750	Every 12 h
Severe	<30	250 to 500	Every 12 h
ESRD patients using dialysis	---	500 to 1,000	[1]Every 24 h

[1] Following dialysis, a 250 to 500 mg supplemental dose is recommended.

HOW SUPPLIED

Keppra™ (levetiracetam) tablets, 250 mg are blue, oblong-shaped, scored, film-coated tablets debossed with "ucb" and "250" on one side. They are supplied in containers of 100 tablets (NDC 50474-591-01), containers of 500 tablets (NDC 50474-951-50) and in hospital unit-dose packages of 100 tablets [10x10] (NDC 50474-591-60).
Keppra™ (levetiracetam) tablets, 500 mg are yellow, oblong-shaped, scored, film-coated tablets debossed with "ucb" and "500" on one side. They are supplied in containers of 100 tablets (NDC 50474-592-01), containers of 500 tablets (NDC 50474-952-50) and in hospital unit-dose packages of 100 tablets [10x10] (NDC 50474-592-60).
Keppra™ (levetiracetam) tablets, 750 mg are orange, oblong-shaped, scored, film-coated tablets debossed with "ucb" and "750" on one side. They are supplied in containers of 100 tablets (NDC 50474-593-01), containers of 500 tablets (NDC 50474-953-50) and in hospital unit-dose packages of 100 tablets [10x10] (NDC 50474-593-60).

STORAGE

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).
[see USP Controlled Room Temperature]

FOR MEDICAL INFORMATION

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