HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KEPPRA XR™ safely and effectively. See full prescribing information for KEPPRA XR.

KEPPRA XR (levetiracetam) extended-release tablets
Initial U.S. Approval: 1999

----------INDICATIONS AND USAGE----------

KEPPRA XR is an antiepileptic drug indicated for adjunctive therapy in the treatment of partial onset seizures in patients ≥16 years of age with epilepsy **(1)**

----------DOSAGE AND ADMINISTRATION----------

Treatment should be initiated with a dose of 1000 mg once daily. The daily dosage may be adjusted in increments of 1000 mg every 2 weeks to a maximum recommended daily dose of 3000 mg **(2)**.

See full prescribing information for use in patients with impaired renal function **(2.1)**.

----------DOSAGE FORMS AND STRENGTHS----------

- 500 mg white, film-coated extended-release tablet **(3)**

----------CONTRAINDICATIONS----------

- None **(4)**

----------WARNINGS AND PRECAUTIONS----------

- **Neuropsychiatric Adverse Reactions:** KEPPRA XR causes somnolence, dizziness, and behavioral abnormalities. The adverse reactions that may be seen in patients receiving KEPPRA XR tablets are expected to be similar to those seen in patients receiving immediate-release KEPPRA tablets. **(5.1)**
- In controlled trials of immediate-release KEPPRA tablets in patients experiencing partial onset seizures, immediate-release KEPPRA causes somnolence and fatigue, coordination difficulties, and behavioral abnormalities (e.g., psychotic symptoms, suicidal ideation, and other abnormalities). **(5.1)**
- **Withdrawal Seizures:** KEPPRA XR must be gradually withdrawn. **(5.2)**

----------ADVERSE REACTIONS----------

- Most common adverse reactions (difference in incidence rate is ≥5% between KEPPRA XR-treated patients and placebo-treated patients and occurred more frequently in KEPPRA XR-treated patients) include: somnolence and irritability **(6.1)**.

To report SUSPECTED ADVERSE REACTIONS, contact UCB, Inc. at 866-822-0068 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------USE IN SPECIFIC POPULATIONS----------

- To enroll in the UCB AED Pregnancy Registry call 888-537-7734 (toll free). To enroll in the North American Antiepileptic Drug Pregnancy Registry call (888) 233-2334 (toll free). **(8.1)**
- A dose adjustment is recommended for patients with impaired renal function, based on the patient's estimated creatinine clearance **(8.6)**.

See 17 for PATIENT COUNSELING INFORMATION
Revised: [09/2008]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed.

1 INDICATIONS AND USAGE

KEPPRA XR™ is indicated as adjunctive therapy in the treatment of partial onset seizures in patients ≥16 years of age with epilepsy.

2 DOSAGE AND ADMINISTRATION

Treatment should be initiated with a dose of 1000 mg once daily. The daily dosage may be adjusted in increments of 1000 mg every 2 weeks to a maximum recommended daily dose of 3000 mg.

2.1 Adult Patients With Impaired Renal Function

KEPPRA XR dosing must be individualized according to the patient's renal function status. Recommended doses and adjustment for dose for adults are shown in Table 1. 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:

$$\text{CLcr} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \times {}^{1}0.85$$

[1.] For female patients

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

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

Table 1: Dosing Adjustment Regimen For Adult Patients With Impaired Renal Function

Group	Creatinine Clearance (mL/min/1.73m^2)	Dosage (mg)	Frequency
Normal	> 80	1000 to 3000	Every 24 h
Mild	50 – 80	1000 to 2000	Every 24 h
Moderate	30 – 50	500 to 1500	Every 24 h
Severe	< 30	500 to 1000	Every 24 h

3 DOSAGE FORMS AND STRENGTHS

KEPPRA XR tablets are white, oblong-shaped, film-coated extended-release tablets imprinted in red with "UCB 500XR" on one side and contain 500 mg levetiracetam.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Neuropsychiatric Adverse Reactions

KEPPRA XR Tablets

In some patients experiencing partial onset seizures, KEPPRA XR causes somnolence, dizziness, and behavioral abnormalities.

In the KEPPRA XR double-blind, controlled trial in patients experiencing partial onset seizures, 7.8% of KEPPRA XR-treated patients experienced somnolence compared to 2.5% of placebo-treated patients. Dizziness was reported in 5.2% of KEPPRA XR-treated patients compared to 2.5% of placebo-treated patients.

A total of 6.5% of KEPPRA XR-treated patients experienced non-psychotic behavioral disorders (reported as irritability and aggression) compared to 0% of placebo-treated patients. Irritability was reported in 6.5% of KEPPRA XR-treated patients. Aggression was reported in 1.3% of KEPPRA XR-treated patients.

No patient discontinued treatment or had a dose reduction as a result of these adverse reactions.

The number of patients exposed to KEPPRA XR was considerably smaller than the number of patients exposed to immediate-release KEPPRA tablets in controlled trials. Therefore, certain adverse reactions observed in the immediate-release KEPPRA controlled trials may also occur in patients receiving KEPPRA XR.

Immediate-Release KEPPRA Tablets

In controlled trials of immediate-release KEPPRA tablets in patients experiencing partial onset seizures, immediate-release KEPPRA causes the occurrence of central nervous system adverse reactions that can be classified into the following categories: 1) somnolence and fatigue, 2) coordination difficulties, and 3) behavioral abnormalities.

In controlled trials of adult patients with epilepsy experiencing partial onset seizures, 14.8% of immediate-release KEPPRA-treated patients reported somnolence, compared to 8.4% of placebo patients. There was no clear dose response up to 3000 mg/day.

In controlled trials of adult patients with epilepsy experiencing partial onset seizures, 14.7% of treated patients reported asthenia, compared to 9.1% of placebo patients.

A total of 3.4% of immediate-release KEPPRA-treated patients experienced coordination difficulties, (reported as either ataxia, abnormal gait, or incoordination) compared to 1.6% of placebo patients.

Somnolence, asthenia and coordination difficulties occurred most frequently within the first 4 weeks of treatment.

In controlled trials of patients with epilepsy experiencing partial onset seizures, 5 (0.7%) immediate-release KEPPRA-treated patients experienced psychotic symptoms compared to 1 (0.2%) placebo patient.

A total of 13.3% of immediate-release KEPPRA patients experienced other behavioral symptoms (reported as aggression, agitation, anger, anxiety, apathy, depersonalization, depression, emotional lability, hostility, irritability, etc.) compared to 6.2% of placebo patients.

In addition, 4 (0.5%) immediate-release KEPPRA-treated patients attempted suicide compared to 0% of placebo patients. One of these patients completed 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 4 weeks and 6 months.

5.2 Withdrawal Seizures

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

5.3 Hematologic Abnormalities

Although there were no obvious hematologic abnormalities observed in treated patients in the KEPPRA XR controlled study, the limited number of patients makes any conclusion tentative. The data from the partial seizure patients in the immediate-release KEPPRA controlled studies should be considered to be relevant for KEPPRA XR-treated patients.

In controlled trials of immediate-release KEPPRA tablets in patients experiencing partial onset seizures, minor, but statistically significant, decreases compared to placebo in total mean RBC count ($0.03 \times 10^6/mm^3$), mean hemoglobin (0.09 g/dL), and mean hematocrit (0.38%), were seen in immediate-release KEPPRA-treated patients. 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% of treated and 1.4% of placebo patients had at least one possibly 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.

5.4 Hepatic Abnormalities

There were no meaningful changes in mean liver function tests (LFT) in the KEPPRA XR controlled trial. No patients were discontinued from the controlled trial for LFT abnormalities.

There were no meaningful changes in mean liver function tests (LFT) in controlled trials of immediate-release KEPPRA tablets in adult patients; 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%) adult epilepsy patient receiving open treatment.

5.5 Laboratory Tests

Although effects on laboratory tests were not clinically significant with KEPPRA XR treatment, it is expected that the data from immediate-release KEPPRA tablets controlled studies would be considered relevant for KEPPRA XR-treated patients.

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

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The prescriber should be aware that the adverse reaction incidence figures in the following table, obtained when KEPPRA XR 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 reaction incidences in the population studied.

KEPPRA XR Tablets

In the well-controlled clinical study using KEPPRA XR in patients with partial onset seizures, the most frequently reported adverse reactions in patients receiving KEPPRA XR in combination with other AEDs, not seen at an equivalent frequency among placebo-treated patients, were irritability and somnolence.

Table 2 lists treatment-emergent adverse reactions that occurred in at least 5% of epilepsy patients treated with KEPPRA XR participating in the placebo-controlled study and were numerically more common than in patients treated with placebo. In this study, either KEPPRA XR or placebo was added to concurrent AED therapy. Adverse reactions were usually mild to moderate in intensity.

Table 2: Incidence (%) Of Treatment-Emergent Adverse Reactions In The Placebo-Controlled, Add-On Study By Body System (Adverse Reactions Occurred In At Least 5% Of KEPPRA XR-Treated Patients And Occurred More Frequently Than Placebo-Treated Patients)

Body System/ Adverse Reaction	KEPPRA XR (N=77) %	Placebo (N=79) %
Gastrointestinal Disorders		
Nausea	5	3
Infections and Infestations		
Influenza	8	4

Nasopharyngitis	7	5
Nervous System Disorders		
Somnolence	8	3
Dizziness	5	3
Psychiatric Disorders		
Irritability	7	0

Discontinuation Or Dose Reduction In The KEPPRA XR Well-Controlled Clinical Study

In the well-controlled clinical study using KEPPRA XR, 5.2% of patients receiving KEPPRA XR and 2.5% receiving placebo discontinued as a result of an adverse event. The adverse reactions that resulted in discontinuation and that occurred more frequently in KEPPRA XR-treated patients than in placebo-treated patients were asthenia, epilepsy, mouth ulceration, rash and respiratory failure. Each of these adverse reactions led to discontinuation in a KEPPRA XR-treated patient and no placebo-treated patients.

Comparison Of Gender, Age And Race

There are insufficient data for KEPPRA XR to support a statement regarding the distribution of adverse experience reports by gender, age and race.

Table 3 lists the adverse reactions seen in the well-controlled studies of immediate-release KEPPRA tablets in adult patients experiencing partial onset seizures. Although the pattern of adverse reactions in the KEPPRA XR study seems somewhat different from that seen in partial onset seizure well-controlled studies for immediate-release KEPPRA tablets, this is possibly due to the much smaller number of patients in this study compared to the immediate-release tablet studies. The adverse reactions for KEPPRA XR are expected to be similar to those seen with immediate-release KEPPRA tablets.

Immediate-Release KEPPRA Tablets

In well-controlled clinical studies of immediate-release KEPPRA tablets as adjunctive therapy to other AEDs in adults with partial onset seizures, the most frequently reported adverse reactions, not seen at an equivalent frequency among placebo-treated patients, were somnolence, asthenia, infection and dizziness.

Table 3 lists treatment-emergent adverse reactions that occurred in at least 1% of adult epilepsy patients treated with immediate-release KEPPRA tablets participating in placebo-controlled studies and were numerically more common than in patients treated with placebo. In these studies, either immediate-release KEPPRA tablets or placebo was added to concurrent AED therapy. Adverse reactions were usually mild to moderate in intensity.

Table 3: Incidence (%) Of Treatment-Emergent Adverse Reactions In Placebo-Controlled, Add-On Studies In Adults Experiencing Partial Onset Seizures By Body System (Adverse Reactions Occurred In At Least 1% Of Immediate-Release KEPPRA-Treated Patients And Occurred More Frequently Than Placebo-Treated Patients)

Body System/ Adverse Reaction	Immediate-release 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		
Somnolence	15	8
Dizziness	9	4
Depression	4	2
Nervousness	4	2
Ataxia	3	1
Vertigo	3	1
Amnesia	2	1
Anxiety	2	1
Hostility	2	1
Paresthesia	2	1
Emotional Lability	2	0
Respiratory System		
Pharyngitis	6	4
Rhinitis	4	3
Cough Increased	2	1
Sinusitis	2	1
Special Senses		
Diplopia	2	1

In addition, the following adverse reactions were seen in other well-controlled studies of immediate-release KEPPRA tablets: balance disorder, disturbance in attention, eczema, hyperkinesia, memory impairment, myalgia, personality disorders, pruritus, and vision blurred.

6.2 Postmarketing Experience

In addition to the adverse reactions listed above for immediate-release KEPPRA tablets *[see Adverse Reactions (6.1)]*, the following adverse events have been identified during postapproval use of immediate-release KEPPRA tablets. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a casual relationship to drug exposure. The listing is alphabetized: abnormal liver function test, hepatic failure, hepatitis, leukopenia, neutropenia, pancreatitis, pancytopenia (with bone marrow suppression identified in some of these cases), suicidal behavior (including completed suicide), thrombocytopenia and weight loss. Alopecia has been reported with immediate-release KEPPRA use; recovery was observed in majority of cases where immediate-release KEPPRA was discontinued.

7 DRUG INTERACTIONS

7.1 General Information

In vitro data on metabolic interactions indicate that KEPPRA XR 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.

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, valproate, oral contraceptive, digoxin, warfarin, probenecid) and through pharmacokinetic screening with immediate-release KEPPRA tablets in the placebo-controlled clinical studies in epilepsy patients. The following are the results of these studies. The potential for drug interactions for KEPPRA XR is expected to be essentially the same as that with immediate-release KEPPRA tablets.

7.2 Phenytoin

Immediate-release KEPPRA tablets (3000 mg daily) had no effect on the pharmacokinetic disposition of phenytoin in patients with refractory epilepsy. Pharmacokinetics of levetiracetam were also not affected by phenytoin.

7.3 Valproate

Immediate-release KEPPRA tablets (1500 mg twice daily) did not alter the pharmacokinetics of valproate in healthy volunteers. Valproate 500 mg twice daily did not modify the rate or extent of levetiracetam absorption or its plasma clearance or urinary excretion. There also was no effect on exposure to and the excretion of the primary metabolite, ucb L057.

7.4 Other Antiepileptic Drugs

Potential drug interactions between immediate-release KEPPRA tablets and other AEDs (carbamazepine, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone and valproate) were also 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 other AEDs and that these AEDs do not influence the pharmacokinetics of levetiracetam.

7.5 Oral Contraceptives

Immediate-release KEPPRA tablets (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.

7.6 Digoxin

Immediate-release KEPPRA tablets (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.

7.7 Warfarin

Immediate-release KEPPRA tablets (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.

7.8 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 immediate-release KEPPRA tablets on probenecid was not studied.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. In animal studies, levetiracetam produced evidence of developmental toxicity, including teratogenic effects, at doses similar to or greater than human therapeutic doses. KEPPRA XR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Oral administration of levetiracetam to female rats throughout pregnancy and lactation led to 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.

Oral administration of levetiracetam to 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 levetiracetam was administered orally to pregnant rats 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 with levetiracetam during the last third of gestation and throughout lactation produced no adverse developmental or maternal effects at oral doses of up to 1800 mg/kg/day (6 times the MRHD on a mg/m^2 basis).

UCB AED Pregnancy Registry

UCB, Inc. has established the UCB AED Pregnancy Registry to advance scientific knowledge about safety and outcomes in pregnant women being treated with all UCB antiepileptic drugs including KEPPRA XR. To ensure broad program access and reach, either a healthcare provider or the patient can initiate enrollment in the UCB AED Pregnancy Registry by calling (888) 537-7734 (toll free). Patients may also enroll in the North American Antiepileptic Drug Pregnancy Registry by calling (888) 233-2334 (toll free).

8.2 Labor And Delivery

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

8.3 Nursing Mothers

Levetiracetam is excreted in breast milk. Because of the potential for serious adverse reactions in nursing infants from KEPPRA XR, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

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

8.5 Geriatric Use

There were insufficient numbers of elderly subjects in controlled trials of epilepsy to adequately assess the effectiveness of KEPPRA XR in these patients. It is expected that the safety of KEPPRA XR in elderly patients 65 and over would be comparable to the safety observed in clinical studies of immediate-release KEPPRA tablets.

Of the total number of subjects in clinical studies of immediate-release 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 immediate-release 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 of immediate-release KEPPRA tablets 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.

8.6 Use In Patients With Impaired Renal Function

The effect of KEPPRA XR on renally impaired patients was not assessed in the well-controlled study. However, it is expected that the effect on KEPPRA XR-treated patients would be similar to the effect seen in well-controlled studies of immediate-release KEPPRA tablets. Caution should be taken in dosing patients with moderate and severe renal impairment and in patients undergoing hemodialysis. The dosage should be reduced in patients with impaired renal function receiving KEPPRA XR [*see Clinical Pharmacology (12.3) and Dosage and Administration (2.1)*].

Clearance of immediate-release levetiracetam is decreased in patients with renal impairment and is correlated with creatinine clearance.

9 DRUG ABUSE AND DEPENDENCE

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

10 OVERDOSAGE

Signs, Symptoms And Laboratory Findings Of Acute Overdosage In Humans

The signs and symptoms for KEPPRA XR overdose are expected to be similar to those seen with immediate-release KEPPRA tablets.

The highest known dose of oral immediate-release KEPPRA received in the clinical development program was 6000 mg/day. Other than drowsiness, there were no adverse reactions 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 immediate-release KEPPRA overdoses in postmarketing use.

Treatment Or Management Of Overdose

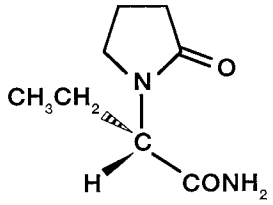
There is no specific antidote for overdose with KEPPRA XR. If indicated, elimination of unabsorbed drug should be attempted by emesis or gastric lavage; usual precautions should be observed to maintain airway. General supportive care of the patient is indicated including monitoring of vital signs and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

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.

11 DESCRIPTION

KEPPRA XR is an antiepileptic drug available as 500 mg (white) extended-release 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. (Solubility limits are expressed as g/100 mL solvent.)

KEPPRA XR tablets contain the labeled amount of levetiracetam. Inactive ingredients: colloidal anhydrous silica, hypromellose, magnesium stearate, polyethylene glycol 6000, polyvinyl alcohol-partially hydrolyzed, titanium dioxide (E171), Macrogol/PEG3350, and talc. The imprinting ink contains shellac, FD&C Red #40, n-butyl alcohol, propylene glycol, titanium dioxide, ethanol, and methanol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism Of Action

The precise mechanism(s) by which levetiracetam exerts its antiepileptic effect is unknown. 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 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.

Levetiracetam at concentrations of up to 10 μM did not demonstrate binding affinity for a variety of known receptors, such as those associated with benzodiazepines, GABA (gamma-aminobutyric acid), glycine, NMDA (N-methyl-D-aspartate), re-uptake sites, and second messenger systems. Furthermore, *in vitro* studies have failed to find an effect of levetiracetam on neuronal voltage-gated sodium or T-type calcium currents and levetiracetam does not appear to directly facilitate GABAergic neurotransmission. However, *in vitro* studies have demonstrated that levetiracetam opposes the activity of negative modulators of GABA- and glycine-gated currents and partially inhibits N-type calcium currents in neuronal cells.

A saturable and stereoselective neuronal binding site in rat brain tissue has been described for levetiracetam. Experimental data indicate that this binding site is the synaptic vesicle protein SV2A, thought to be involved in the regulation of vesicle exocytosis. Although the molecular significance of levetiracetam binding to synaptic vesicle protein SV2A is not understood, levetiracetam and related analogs showed a rank order of affinity for SV2A which correlated with the potency of their antiseizure activity in audiogenic seizure-prone mice. These findings suggest that the interaction of levetiracetam with the SV2A protein may contribute to the antiepileptic mechanism of action of the drug.

12.3 Pharmacokinetics

Overview
Bioavailability of Keppra XR tablets is similar to that of the Keppra IR Tablets**.** The pharmacokinetics (AUC and C_{max}) were shown to be dose proportional after single dose administration of 1000 mg, 2000 mg, and 3000 mg extended-release levetiracetam. Plasma half-life of extended-release levetiracetam is approximately 7 hours.

Levetiracetam is almost completely absorbed after oral administration. The pharmacokinetics of levetiracetam are linear and time-invariant, with low intra- and inter-subject variability. Levetiracetam is not significantly 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. The half-life is increased in the elderly (primarily due to impaired renal clearance) and in subjects with renal impairment.

Absorption and Distribution

Extended-release levetiracetam peak plasma concentrations occur in about 4 hours. The time to peak plasma concentrations is about 3 hours longer with extended-release levetiracetam than with immediate-release tablets.

Single administration of two 500 mg extended-release levetiracetam tablets once daily produced comparable maximal plasma concentrations and area under the plasma concentration versus time as did the administration of one 500 mg immediate-release tablet twice daily in fasting conditions. After multiple dose extended-release levetiracetam tablets intake, extent of exposure (AUC_{0-24}) was similar to extent of exposure after multiple dose immediate-release tablets intake. C_{max} and C_{min} were lower by 17% and 26% after multiple dose extended-release levetiracetam tablets intake in comparison to multiple dose immediate-release tablets intake. Intake of a high fat, high calorie breakfast before the administration of extended-release levetiracetam tablets resulted in a higher peak concentration, and longer median time to peak. The median time to peak (T_{max}) was 2 hours longer in the fed state.

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% of dose) 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 Use in Specific Populations (8.6) and Dosage and Administration (2.1)*].

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. The pharmacokinetics of immediate-release levetiracetam are linear over the dose range of 500-5000 mg. 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.

Potential pharmacokinetic interactions of or with immediate-release levetiracetam were assessed in clinical pharmacokinetic studies (phenytoin, valproate, warfarin, digoxin, oral contraceptive, probenecid) and through pharmacokinetic screening in the placebo-controlled clinical studies in epilepsy patients [*see Drug Interactions (7)*]. The potential for drug interactions for extended-release levetiracetam is expected to be similar to that with immediate-release levetiracetam.

Special Populations

Elderly

There are insufficient pharmacokinetic data to specifically address the use of extended-release levetiracetam in the elderly population.

Pharmacokinetics of immediate-release 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

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

Gender

Extended-release levetiracetam C_{max} was 21-30% higher and AUC was 8-18% higher in women (N=12) 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 with extended-release or immediate-release levetiracetam. Cross study comparisons involving Caucasians (N=12) and Asians (N=12), however, show that pharmacokinetics of immediate-release levetiracetam were comparable between the two races.

Renal Impairment

The effect of KEPPRA XR on renally impaired patients was not assessed in the well-controlled study. However, it is expected that the effect on KEPPRA XR-treated patients would be similar to that seen in well-controlled studies of immediate-release KEPPRA tablets. In patients with end stage renal disease on dialysis, it is recommended that immediate-release KEPPRA be used instead of KEPPRA XR.

The disposition of immediate-release levetiracetam was studied in adult 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; immediate-release levetiracetam should be given to patients on dialysis [*see Dosage and Administration (2.1)*].

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.

13 NONCLINICAL TOXICOLOGY

13.1 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 (ucb 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 oral doses up to 1800 mg/kg/day (approximately 6 times the maximum recommended human dose on a mg/m^2 or exposure basis).

13.2 Animal Toxicology And/Or Pharmacology

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

14 CLINICAL STUDIES

The effectiveness of the immediate-release formulation 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 904 patients who had refractory partial onset seizures with or without secondary generalization for at least two years and had taken two or more classical AEDs.

The effectiveness of KEPPRA XR as adjunctive therapy (added to other antiepileptic drugs) was established in one multicenter, randomized, double-blind, placebo-controlled clinical study across 7 countries in patients who had refractory partial onset seizures with or without secondary generalization. Patients enrolled had at least eight partial seizures with or without secondary generalization during the 8-week baseline period and at least two partial seizures in each 4-week interval of the baseline period. Patients were taking a stable dose regimen of at least one and could take a maximum of three AEDs. After a prospective baseline period of 8 weeks, 158 patients were randomized to placebo (N=79) or KEPPRA XR (2x500 mg tablets) (N=79) given once daily over a 12-week treatment period.

The primary efficacy endpoint was the percent reduction over placebo in mean weekly frequency of partial onset seizures. The median percent reduction in weekly partial onset seizure frequency from baseline over the treatment period was 46.1% in the KEPPRA XR 1000 mg treatment group (N=74) and 33.4% in the placebo group (N=78). The estimated percent reduction over placebo in weekly partial onset seizure frequency over the treatment period was 14.4% (statistically significant).

The relationship between the effectiveness of the same daily dose of KEPPRA XR and immediate-release KEPPRA has not been studied and is unknown.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

KEPPRA XR 500 mg tablets are white, oblong-shaped, film-coated tablets imprinted with “UCB 500XR” in red on one side. They are supplied in white HDPE bottles containing 60 tablets (NDC 50474-598-66).

16.2 Storage

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

17 PATIENT COUNSELING INFORMATION

Patients should be instructed to only take KEPPRA XR as prescribed and to swallow the tablets whole. They should not be chewed, broken, or crushed.

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

Patients should be advised that KEPPRA XR may cause irritability and aggression.

In addition, patients should be advised that they may experience changes in behavior that have been seen with other formulations of KEPPRA, which include agitation, anger, anxiety, apathy, depression, hostility, irritability and, in rare cases, psychotic symptoms and/or suicidal ideation. Patients should be advised to immediately report any symptoms of depression and/or suicidal ideation to their prescribing physician.

Physicians should advise patients and caregivers to read the patient information leaflet which appears as the last section of the labeling.

KEPPRA XR manufactured for
UCB, Inc.
Smyrna, GA 30080

PATIENT INFORMATION

KEPPRA XR™ (pronounced *KEPP-ruh XR)* (levetiracetam)
500 mg extended-release tablets

Read the Patient Information that comes with KEPPRA XR before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your condition or your treatment.

Before taking your medicine, make sure you have received the correct medicine. Compare the name above with the name on your bottle and the appearance of your medicine with the description of KEPPRA XR provided below. Contact your pharmacist immediately if you believe a dispensing error may have occurred.

500 mg KEPPRA XR tablets are white, oblong-shaped, film-coated tablets marked with "UCB 500XR" in red on one side.

What is KEPPRA XR?
KEPPRA XR is a medicine taken by mouth once daily that is used with other medicines to treat partial onset seizures in patients 16 years of age and older with epilepsy.

What should I tell my healthcare provider before starting KEPPRA XR?
Tell your healthcare provider about all of your medical conditions, including if you:

- **have kidney disease.** You may need a lower dose of KEPPRA XR.
- **are pregnant or planning to become pregnant.** It is not known if KEPPRA XR can harm your unborn baby. If you use KEPPRA XR while you are pregnant, ask your healthcare provider about being in the UCB AED Pregnancy Registry. You can join this registry by calling (888) 537-7734 (toll free). You may also join the North American Antiepileptic Drug Pregnancy Registry by calling (888) 233-2334 (toll free).
- **are breast feeding.** KEPPRA XR can pass into your milk and may harm your baby. You should choose to either take KEPPRA XR or breast feed, but not both.

Tell your healthcare provider about all the medicines you take, including prescription, nonprescription, vitamins, and herbal supplements. Tell your healthcare provider about any allergies you may have.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist each time you get a new medicine.

How should I take KEPPRA XR?

- Take KEPPRA XR exactly as prescribed. KEPPRA XR is usually taken once a day. Take KEPPRA XR at the same time each day.
- Your healthcare provider may start you on a lower dose of KEPPRA XR and increase it as your body gets used to the medicine.
- Take KEPPRA XR with or without food. Swallow the tablets whole. Do not chew, break, or crush tablets.
- If you miss a dose of KEPPRA XR, do not double your next dose to make up for the missed dose. If it has only been a few hours since your missed dose, take KEPPRA XR as soon as you remember then return to your regular schedule. If it is almost time for the next dose, skip the missed dose and resume your regular schedule. Talk with your healthcare provider for more detailed instructions.
- If you take too much KEPPRA XR or overdose, call your local Poison Control Center or emergency room right away.
- Do not stop taking KEPPRA XR or any other seizure medicine unless your healthcare provider told you to. Stopping a seizure medicine all at once can cause seizures that will not stop (status epilepticus), a very serious problem.
- Tell your healthcare provider if your seizures get worse or if you have any new types of seizures.

What should I avoid while taking KEPPRA?
Do not drive, operate machinery or do other dangerous activities until you know how KEPPRA XR affects you. KEPPRA XR may make you dizzy or sleepy.

What are the possible side effects of KEPPRA XR?

KEPPRA XR may cause the following serious problems:
- extreme sleepiness and dizziness
- behavior changes such as irritability and aggression

In addition, the following serious problems have been seen with other formulations of KEPPRA:
- extreme sleepiness, tiredness, and weakness
- problems with muscle coordination (problems walking and moving)
- mood and behavior changes such as aggression, agitation, anger, anxiety, apathy, mood swings, depression, hostility, and irritability. A few people may get psychotic symptoms such as hallucinations (seeing or hearing things that are really not there), delusions (false or strange thoughts or beliefs) and unusual behavior. A few people may get thoughts of suicide (thoughts of killing yourself).

Call your healthcare provider right away if you get any of these symptoms.

The most common side effects with KEPPRA XR are:
- sleepiness
- irritability

These side effects could happen at any time but happen most often within the first four weeks of treatment.

These are not all the side effects of KEPPRA XR. For more information, ask your healthcare provider or pharmacist. If you get any side effects that concern you, call your healthcare provider.

How should I store KEPPRA XR?
- Store KEPPRA at room temperature away from heat and light.
- **Keep KEPPRA XR and all medicines out of the reach of children.**

General information about KEPPRA XR.
Medicines are sometimes prescribed for conditions other than those described in patient information leaflets. Do not use KEPPRA XR for a condition for which it was not prescribed. Do not give your KEPPRA XR to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about KEPPRA XR. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about KEPPRA XR that is written for healthcare professionals.

What are the ingredients of KEPPRA XR?
KEPPRA XR tablets contain the labeled amount of levetiracetam. Inactive ingredients: colloidal anhydrous silica, hypromellose, magnesium stearate, polyethylene glycol 6000, polyvinyl alcohol-partially hydrolyzed, titanium dioxide (E171), Macrogol/PEG3350, and talc. The imprinting ink contains shellac, FD&C Red #40, n-butyl alcohol, propylene glycol, titanium dioxide, ethanol, and methanol.

KEPPRA XR does not contain lactose or gluten.
Rx Only

This patient leaflet has been approved by the US Food and Drug Administration.

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