

PRESCRIBING INFORMATION

Keppra

Film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Keppra 250 mg film-coated tablets

Keppra 500 mg film-coated tablets

Keppra 1,000 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 250 mg, 500 mg, 1,000 mg levetiracetam.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Keppra is indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults and children from 4 years of age with epilepsy.

4.2 Posology and method of administration

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

Adults (≥18 years) and adolescents (12 to 17 years) weighing 50 kg or more

The initial therapeutic dose is 500 mg twice daily. This dose can be started on the first day of treatment.

Depending upon the clinical response and tolerability, the daily dose can be increased up to 1,500 mg twice daily. Dose changes can be made in 500 mg twice daily increments or decrements every two to four weeks.

Elderly (65 years and older)

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

Children (4 to 11 years) and adolescents (12 to 17 years) weighing less than 50 kg

The initial therapeutic dose is 10 mg/kg twice daily.

Depending upon the clinical response and tolerability, the dose can be increased up to 30 mg/kg twice daily. Dose changes should not exceed increments or decrements of 10 mg/kg twice daily every two weeks. The lowest effective dose should be used.

Dosage in children weighing 50 kg or more is the same as in adults.

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

Dosage recommendations for children and adolescents:

Weight	Starting dose: 10 mg/kg twice daily	Maximum dose: 30 mg/kg twice daily
15 kg ⁽¹⁾	150 mg twice daily	450 mg twice daily
20 kg ⁽¹⁾	200 mg twice daily	600 mg twice daily
25 kg	250 mg twice daily	750 mg twice daily
From 50 kg ⁽²⁾	500 mg twice daily	1,500 mg twice daily

⁽¹⁾ Children weighing 20 kg or less should preferably start the treatment with Keppra 100 mg/ml oral solution.
⁽²⁾ Dosage in children and adolescents weighing 50 kg or more is the same as in adults.

Infants and children less than 4 years of age

There are insufficient data to recommend the use of levetiracetam in children under 4 years of age.

Patients with renal impairment

The daily dose must be individualised according to renal function.

For adult patients, refer to the following table and adjust the dose as indicated. 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:

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

Dosing adjustment for adult patients with impaired renal function:

Group	Creatinine clearance (ml/min)	Dosage and frequency
Normal	>80	500 to 1,500 mg twice daily
Mild	50-79	500 to 1,000 mg twice daily
Moderate	30-49	250 to 750 mg twice daily
Severe	<30	250 to 500 mg twice daily
End-stage renal disease patients undergoing dialysis ⁽¹⁾	-	500 to 1,000 mg once daily ⁽²⁾

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

For children with renal impairment, the levetiracetam dose needs to be adjusted based on 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 to 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 <70 ml/min.

4.3 Contraindications

Hypersensitivity to levetiracetam or other pyrrolidone derivatives or any of the excipients.

4.4 Special warnings and special precautions for use

In accordance with current clinical practice, if Keppra has to be discontinued it is recommended to withdraw it gradually (e.g. in adults: 500 mg twice daily decrements every two to four weeks; in children: dose decrease should not exceed decrements of 10 mg/kg twice daily every two weeks).

In a study reflecting clinical practice, the concomitant antiepileptic medication could be withdrawn in a limited number of patients who responded to levetiracetam adjunctive therapy (36 adult patients out of 69).

Available data in children did not suggest impact on growth and puberty. However, long term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children remain unknown.

An increase in seizure frequency of more than 25% was reported in 14% of levetiracetam treated adult and paediatric patients, whereas it was reported in 26% and 21% of placebo treated adult and paediatric patients, respectively.

The administration of Keppra to patients with renal impairment may require dose adjustment. In patients with severely impaired hepatic function, assessment of renal function is recommended before dose selection (see section 4.2 "Posology").

4.5 Interaction with other medicinal products and other forms of interaction

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 medicinal product interactions in paediatric patients receiving up to 60 mg/kg/day levetiracetam.

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 and valproate. However, data suggested that enzyme-inducing antiepileptic medicinal products increase levetiracetam clearance by 22%. Dosage adjustment is not required.

Probenecid (500 mg four times daily), a renal tubular secretion blocking agent, has been shown to inhibit the renal clearance of the primary metabolite but not of levetiracetam. Nevertheless, the concentration of this metabolite remains low. It is expected that other medicinal products excreted by active tubular secretion could also reduce the renal clearance of the metabolite. The effect of levetiracetam on probenecid was not studied and the effect of levetiracetam on other actively secreted medicinal products, e.g. NSAIDs, sulfonamides and methotrexate, is unknown. Levetiracetam 1,000 mg daily did not influence the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel); endocrine parameters (luteinizing hormone and progesterone) were not modified. Levetiracetam 2,000 mg daily did not influence the pharmacokinetics of digoxin and warfarin; prothrombin times were not modified. Co-administration with digoxin, oral contraceptives and warfarin did not influence the pharmacokinetics of levetiracetam.

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

The extent of absorption of levetiracetam was not altered by food, but the rate of absorption was slightly reduced.

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

4.6 Pregnancy and lactation

There are no adequate data from the use of Keppra in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Keppra should not be used during pregnancy unless clearly necessary. Discontinuation of antiepileptic treatments may result in exacerbation of the disease which could be harmful to the mother and the foetus.

Levetiracetam is excreted in human breast milk. Therefore, breast-feeding is not recommended.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Due to possible different individual sensitivity, some patients might experience somnolence or other central nervous system related symptoms, at the beginning of treatment or following a dose increase. Therefore, caution is recommended in those patients when performing skilled tasks, e.g. driving vehicles or operating machinery.

4.8 Undesirable effects

Pooled safety data from clinical studies conducted in adult patients showed that 46.4% of the patients in the Keppra group and 42.2% of the patients in the placebo group experienced undesirable effects. Serious undesirable effects were experienced in 2.4% of the patients in the Keppra group and 2.0% of the patients in the placebo group. The most commonly reported undesirable effects were somnolence, asthenia and dizziness. In the pooled safety analysis, there was no clear dose-response relationship, but incidence and severity of the central nervous system related undesirable effects decreased over time.

A study conducted in paediatric patients (4 to 16 years) showed that 55.4% of the patients in the Keppra group and 40.2% of the patients in the placebo group experienced undesirable effects. Serious undesirable effects were experienced in 0.0% of the patients in the Keppra group and 1.0% of the patients in the placebo group. The most commonly reported undesirable effects were somnolence, hostility, nervousness, emotional lability, agitation, anorexia, asthenia and headache in the paediatric population. Safety results in paediatric patients were consistent with the safety profile of levetiracetam in adults except for behavioural and psychiatric adverse events 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.

Undesirable effects reported in clinical studies (adults and children) or from post-marketing experience are listed in the following table per System Organ Class and per frequency. For clinical trials, the frequency is defined as follows: very common: >10%; common: >1-10%; uncommon: >0.1%-1%; rare: 0.01%-0.1%; very rare: <0.01%, including isolated reports. Data from post-marketing experience are insufficient to support an estimate of their incidence in the population to be treated.

General disorders and administration site conditions	
<i>Very common:</i>	Asthenia
Nervous system disorders	
<i>Very common:</i>	Somnolence
<i>Common:</i>	Amnesia, ataxia, convulsion, dizziness, headache, hyperkinesia, tremor
Psychiatric disorders	
<i>Common:</i>	Agitation, depression, emotional lability, hostility, insomnia, nervousness, personality disorders, abnormal thinking
<i>Post-marketing experience:</i>	Abnormal behaviour, aggression, anger, anxiety, confusion, hallucination, irritability, psychotic disorder, suicide, suicide attempt and suicidal ideation
Gastrointestinal disorders	
<i>Common:</i>	Diarrhoea, dyspepsia, nausea, vomiting
Metabolism and nutrition disorders	
<i>Common:</i>	Anorexia. The risk of anorexia is higher when topiramate is co-administered with levetiracetam.
Ear and labyrinth disorders	
<i>Common:</i>	Vertigo

Eye disorders	
Common:	Diplopia
Injury, poisoning and procedural complications	
Common:	Accidental injury
Infections and infestations	
Common:	Infection
Respiratory, thoracic and mediastinal disorders	
Common:	Increased cough
Skin and subcutaneous tissue disorders	
Common:	Rash
Post-marketing experience:	Alopecia: in several cases, recovery was observed when Keppra was discontinued.
Blood and lymphatic system disorders	
Post-marketing experience:	Leukopenia, neutropenia, pancytopenia, thrombocytopenia.

4.9 Overdose

Symptoms

Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with Keppra overdoses.

Management of overdose

After an acute overdose, the stomach may be emptied by gastric lavage or by induction of emesis. There is no specific antidote for levetiracetam. Treatment of an overdose will be symptomatic and may include haemodialysis. The dialyser extraction efficiency is 60% for levetiracetam and 74% for the primary metabolite.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, ATC code: N03AX14

The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of α -ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances.

Mechanism of action

The mechanism of action of levetiracetam still remains to be fully elucidated but appears to be different from the mechanisms of current antiepileptic medicinal products. *In vitro* and *in vivo* experiments suggest that levetiracetam does not alter basic cell characteristics and normal neurotransmission.

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

Pharmacodynamic effects

Levetiracetam induces seizure protection in a broad range of animal models of partial and primarily generalised seizures without having a pro-convulsant effect. The primary metabolite is inactive.

In man, an activity in both partial and generalised epilepsy conditions (epileptiform discharge/photoparoxysmal response) has confirmed the broad spectrum of the preclinical pharmacological profile.

5.2 Pharmacokinetic properties

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

Due to its complete and linear absorption, plasma levels can be predicted from the oral dose of levetiracetam expressed as mg/kg bodyweight. Therefore, there is no need for plasma level monitoring of levetiracetam.

A significant correlation between saliva and plasma concentrations has been shown in adults and children (ratio of saliva/plasma concentrations ranged from 1 to 1.7 for oral tablet formulation and after 4 hours post-dose for 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 and 43 µg/ml following a single 1,000 mg dose and repeated 1,000 mg twice daily dose, respectively.

The extent of absorption is dose-independent and is not altered by food.

Distribution

No tissue distribution data are available in humans.

Neither levetiracetam nor its primary metabolite are significantly bound to plasma proteins (<10%).

The volume of distribution of levetiracetam is approximately 0.5 to 0.7 l/kg, a value close to the total body water volume.

Biotransformation

Levetiracetam is not extensively metabolised in humans. The major metabolic pathway (24% of the dose) is an enzymatic hydrolysis of the acetamide group. Production of the primary 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 blood cells. 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 primary metabolite.

In vitro, levetiracetam and its primary metabolite have been shown not to inhibit the major human liver cytochrome P450 isoforms (CYP3A4, 2A6, 2C8/9/10, 2C19, 2D6, 2E1 and 1A2), glucuronyl transferase (UGT1*6, UGT1*1 and UGT [pl 6.2]) and epoxide hydroxylase activities. In addition, levetiracetam does not affect the *in vitro* glucuronidation of valproic acid.

In human hepatocytes in culture, levetiracetam did not cause enzyme induction. 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 (approximately 93% of the dose was excreted within 48 hours). Excretion via faeces accounted for only 0.3% of the dose.

The cumulative urinary excretion of levetiracetam and its primary metabolite accounted for 66% and 24% of the dose, respectively, during the first 48 hours.

The renal clearance of levetiracetam and ucb L057 is 0.6 and 4.2 ml/min/kg, respectively, indicating that levetiracetam is excreted by glomerular filtration with subsequent tubular reabsorption and that the primary metabolite is also excreted by active tubular secretion in addition to glomerular filtration. Levetiracetam elimination is correlated to creatinine clearance.

Elderly

In the elderly, the half-life is increased by about 40% (10 to 11 hours). This is related to the decrease in renal function in this population (see section 4.2).

Children (4 to 12 years)

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

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

Infants and children (1 month to 4 years)

Following single dose administration (20 mg/kg) of a 100 mg/ml oral solution to epileptic children (1 month to 4 years), levetiracetam was rapidly absorbed and peak plasma concentrations were observed approximately 1 hour after dosing. The pharmacokinetic results indicated that the half-life was shorter (5.3 h) than for adults (7.2 h) and apparent clearance was faster (1.5 ml/min/kg) than for adults (0.96 ml/min/kg).

Renal impairment

The apparent body clearance of both levetiracetam and of its primary metabolite is correlated to the creatinine clearance. It is therefore recommended to adjust the maintenance daily dose of Keppra, based on creatinine clearance in patients with moderate and severe renal impairment (see section 4.2).

In anuric end-stage renal disease adult subjects the half-life was approximately 25 and 3.1 hours during interdialytic and intradialytic periods, respectively.

The fractional removal of levetiracetam was 51% during a typical 4-hour dialysis session.

Hepatic impairment

In subjects with mild and moderate hepatic impairment, there was no relevant modification of the clearance of levetiracetam. In most subjects with severe hepatic impairment, the clearance of levetiracetam was reduced by more than 50% due to a concomitant renal impairment (see section 4.2).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenicity. Although no evidence for carcinogenicity was seen, the potential carcinogenicity has not been fully evaluated due to some shortcomings in the studies performed.

Adverse effects not observed in clinical studies but seen in the rat and to a lesser extent in the mouse at exposure levels similar to human exposure levels and with possible relevance for clinical use were liver changes, indicating an adaptive response such as increased weight and centrilobular hypertrophy, fatty infiltration and increased liver enzymes in plasma.

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 up to 1,800 mg/kg/day corresponding to 30 times the maximum recommended human dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

Sodium croscarmellose, colloidal anhydrous silica, macrogol 6000, magnesium stearate

Film-coating Opadry

Keppra 250 mg Opadry 85F20694 contains

Polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc, indigo carmine aluminium lake (E132).

Keppra 500 mg Opadry 85F32004 contains:

Polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc, iron oxide yellow (E172).

Keppra 1,000 mg Opadry 85F18422 contains:

Polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc.

6.2 Incompatibilities

Not applicable.

6.3 Special precautions for storage

Do not store above 25°.

6.4 Instructions for use and handling

No special requirements.

7. MANUFACTURER

UCB S.A. Allée de la Recherche 60
B-1070 Bruxelles
Belgium

8. IMPORTER

CTS Ltd., 4 Haharash St., Hod-Hasharon

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in November 2006

KEPP TAB PHY SH 150107