CIA72197A

Keppra® 500 mg
levetiracetam

film coated tablets

NAME OF THE MEDICINAL PRODUCT: Keppra 500 mg film-coated tablets

PHARMACEUTICAL FORM AND STRENGTH
Film-coated tablet.
Each film-coated tablet contains 500 mg levetiracetam

FORMULA
Levetiracetam 500 mg, Sodium croscarmellose, Macrogol 6000, Colloidal anhydrous silica, Magnesium stearate, Opadry 85F32004

MARKETING AUTORIZATION HOLDER
UCB Pharma SA, 60, Allée de la Recherche, 1070 Brussels. Belgium

PHARMACOTHERAPEUTIC GROUP: Antiepileptics

THERAPEUTIC INDICATIONS
Keppra is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy.
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.
- in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.
- in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy.

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.
- Monotherapy

Adults and adolescents from 16 years of age
The recommended starting dose is 250 mg twice daily which should be increased to an initial therapeutic dose of 500 mg twice daily after two weeks. The dose can be further increased by 250 mg twice daily every two weeks depending upon the clinical response. The maximum dose is 1500 mg twice daily.
- Add-on therapy

Adults (≥18 years) 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 increases or decreases every two to four weeks.
Elderly (from 65 years old)
Adjustment of the dose is recommended in elderly patients with compromised renal function (see "Patients with renal impairment" below).
Children aged 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 increases or decreases of 10 mg/kg twice daily every two weeks. The lowest effective dose should be used.
Dosage in children 50 kg or greater is the same as in adults.
The physician should prescribe the most appropriate pharmaceutical form and strength according to weight and dose.

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	1500 mg twice daily

[1] Children 20 kg or less should preferably start the treatment with Keppra 100 mg/ml oral solution

[2] Dosage in children and adolescents 50 kg or more is the same as in adults

Infants and children less than 4 years:
Keppra is not recommended for use in children below 4 years of age due to insufficient data on safety and efficacy.
Patients with renal impairment
The daily dose must be individualised according to renal function. For adult patient, 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:

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

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

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

Dosing adjustment for adult patients with impaired renal function

Group	Creatinine clearance (ml/min/1.73 m^2)	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, levetiracetam dose needs to be adjusted based on the renal function as levetiracetam clearance is related to renal function. This recommendation is based on a study in adult renally impaired patients.

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

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

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 decreases twice daily every two to four weeks; in children: dose decrease should not exceed 10 mg/kg twice daily every two weeks).
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 with partial onset seizures, whereas it was reported in 26 % and 21 % of placebo treated adult and paediatric patients, respectively. When Keppra was used to treat primary generalised tonic-clonic seizures in adults and adolescents with idiopathic generalised epilepsy, there was no effect on the frequency of absences. 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 posology and method of administration).
Suicide, suicide attempt and suicidal ideation have been reported in patients treated with levetiracetam. Patients should be advised to immediately report any symptoms of depression and/or suicidal ideation to their prescribing physician.

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.
As in adults, there is no 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 orally administered levetiracetam did not influence the steady-state serum concentrations of concomitantly administered carbamazepine and valproate. However, data suggested a 22 % higher levetiracetam clearance in children taking enzyme-inducing antiepileptic medicinal products. 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.

PREGNANCY AND LACTATION
There are no adequate data from the use of Keppra in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for human is unknown.
Keppra should not be used during pregnancy unless clearly necessary. As with other antiepileptic drugs, physiological changes during pregnancy may affect levetiracetam concentration. There have been reports of decreased levetiracetam concentration during pregnancy. 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.

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, especially 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. Patients are advised not to drive or use machines until it is established that their ability to perform such activities is not affected.

UNDESIRABLE EFFECTS

Like all medicines, Keppra can cause side effects, although not everybody gets them.

Tell your doctor if you have any of the following and they worry you.

Very common side effects (>10%) reported with Keppra are:

- somnolence (sleepiness);
- asthenia/fatigue (tiredness).

Common side effects (>1%–10%) reported with Keppra are:

- nervous system disorders: dizziness (sensation of unsteadiness), convulsion, headache, hyperkinesia (hyperactivity), ataxia (impaired coordinated movements), tremor (involuntary trembling), amnesia (loss of memory), balance disorder (equilibrium disorder), disturbance in attention (loss of concentration), memory impairment (forgetfulness);
- psychiatric disorders: agitation, depression, emotional instability/mood swings, hostility or aggression, insomnia, nervousness or irritability, personality disorders (behavioral problems), thinking abnormal (slow thinking, unable to concentrate);
- digestive disorders: abdominal pain; nausea, dyspepsia (indigestion), diarrhoea, vomiting;
- nutrition disorders: anorexia (loss of appetite), weight increase,
- ear and labyrinth disorders: vertigo (sensation of rotation);
- eye disorders: diplopia (double vision), vision blurred;
- musculoskeletal and connective tissue disorders: myalgia (muscle pain);
- injury: accidental injury;
- infections: infection, nasopharyngitis;
- respiratory disorders: cough (increase of pre-existing cough);
- skin disorders: rash, eczema, pruritus;
- blood disorders: decreased number of blood platelets.

Other side effects reported with Keppra are:

- nervous system disorders: paraesthesia (tingling);
- psychiatric disorders: abnormal behaviour, anger, anxiety, confusion, hallucination, mental disorder, suicide, suicide attempt and suicidal ideation (thoughts of killing yourself);
- digestive disorders: pancreatitis, hepatic failure, hepatitis, liver function test abnormal;
- nutrition disorders: weight loss;
- skin disorders: hair loss;
- blood disorders: decreased number of red blood cells, and/or white blood cells.

Some of the side effects like sleepiness, tiredness and dizziness may be more common at the beginning of the treatment or at dosage increase. These effects should however decrease over time.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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.

INCOMPATIBILITIES: Not applicable.

STORAGE CONDITIONS AND EXPIRY DATE

Store below 25 °C.

Keep out of the reach and sight of children.

Do not use after the expiry date stated on the carton box and blister.

NATURE AND CONTENTS OF CONTAINER

Keppra 500 mg film coated tablets are packaged in aluminium/PVC blisters placed into cardboard boxes containing 30 or 100 film coated tablets.

Manufactured by: UCB PHARMA SA, BRAINE-L'ALLEUD · BELGIUM

CIA72197A

(ان هـــذا الـــدواء)

- الدواء مستحضر يؤثر على صحتك واستهلاكه خلافا للتعليمات يعرضك للخطر
- اتبع بدقه وصفة الطبيب وطريقة الاستعمال المنصوص عليها وتعليمات الصـــيدلانى الـذى صرفها لك .
- فالطبيب والصيدلانى هما الخبيران بالدواء وبنفعه وضرره .
- لاتقطع مدة العلاج المحدده لك من تلقاء نفسك .
- لاتكرر صرف الدواء بدون وصفه طبيه .

لاتترك الادويه فى متناول ايدى الاطفال

مجلس وزراء الصحة العرب
واتحاد الصيادلة العرب

THIS IS A MEDICAMENT

– Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

– Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

– The Doctor and the Pharmacist are experts in medicine, its benefits and risks.

– Do not by yourself interrupt the period of treatment prescribed for you.

– Do not repeat the same prescription without consulting your Doctor.

Council of Arab Health Ministers
Union of Arab Pharmacists