KEPPRA®
Film coated tablet
COMPOSITION
Each film-coated tablet contains 250 mg Levetiracetam Each film-coated tablet contains 500 mg Levetiracetam Each film-coated tablet contains 1000 mg Levetiracetam

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of u.,-ethyl- 2- oxo- 't-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substance.

Mechanism of action
The mechanism of actiQrt of levetiracetam is unknown, but appears to be unrelated to the mechanism of current drugs. In vitro and in vivo experiments suggest that levetiracetam does not alter basic cell characteristics and normal neurotransmission.

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

In man, an activity in both _ partial and generalized epilepsy conditions (epileptiform discharge/ photaparoxysmal response) have confirmed the broad spectrum of the preclinical pharmacological profile.

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 : elevant 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 level can be predicted from .. .m.. the oral dose of levetiracetam expressed as mg/kg bodyweight. Th~ce;fore _ there is no need for plasma level monitorina of levetiracetam.

Absorption
Levetiracetam is rapidly absorbed after oral administration. Oral absolute- bioavailibility is close to 100 %. Peak plasma concentration (Cmax) are achieved at 1.3 hours after dosing. Steady-state is achieved after two days of a twice daily administration schedule.
Peak concentrations (Cmax) are typically 31 and 43 pg/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 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 metabolized 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 P45o isoforms. Hydrolysis of the acetamide group was measurable in a large number of tissue including blood cells. The metabolite ucb L057 is pharmacologically inactive.

The 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 the pyrrolidone ring (0.9'% of the dose). Other unidentified components accounted only for 0.6 % of the dose. No enantiomeric interconversion was evidenced in vivo for either levetiracetam nor its primary metabolite.
In vitro, levetiracetam and its.primary metabolite have been shown not to inhibit the major human liver cytochrome P45oisoform (CYP3A4, 2A6, 2C8/9/10, 2C19, 2D6, 2E1 and 1A2), glucuronyl transferase (UGT1*6, UGT*1 and UGT [p16.2]) and epoxide hydroxylase activities. In addition, levetiracetam does not affect the in vitro glucuronidation of valproic acid.
In human hepatocytes in culture, (evetiracetam did not cause enzyme induction. Therefore, the interaction of Keppra with other substances, or vice iersa, 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 4lomerular 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.

Children (6 to 12 years)

Following single dose administration (20 mg/kg) to epileptic children, the halflife of levetiracetam was 6.0 hours. The apparent body clearance was approximately 30 % higher than in epileptic adults.

Renal impairment

The apparent body clearance of both Cevetiracetam 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.
In anuric end-stage renal disease 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 tevetiracetam was reduced by more than 50 % due to a concomitant renal impairment.

Preclinicat 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 potentioal 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 serum enzymes.

In reproductive toxicity studies in the rat, levetiracetam induced , developmental toxicity (increase in skeletal variation/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.

THERAPEUTIC INDICATIONS
Keppra is indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalization in patients with 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.

Adults and adolescents older than 16 years
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 tolerance, the daily dose can be increased up to 1,500 mg twice daily. Dose changes can made in 500 mg twice daily increments or decrements every two to four weeks.

Elderly (from 65 years old)
Adjustment of the dose is recommended is elderly patients with compromised renal function (see "Patients with renal impairment" below)

Children
There are insufficient data to recommended the use of Levetiracetam children and adolescents under 16 years of age.

Patients with renal impairment
The daily dose must be individualized according to renal function. Refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate to the patient's creatinine clearance (CLcr) in ml/ min is needed. The CLcr im mlf min may be estimated from serum creatinine (mg/dl) determination using the following formula:

$$CLcr = \frac{[140 - age(years)] \times weight\ (kg)}{72 \times serum\ creatihine\ (mg/dl)} \quad (\times 0{,}85\ for\ women)$$

Dosing Adjustments for 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	250-500 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 Leveti racetam
(2). Following dialysis, a 250 to 500 mg supplemental dose is recommended

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. There-'ore a 50% reduction of the daily maintenance dose is recommended when the creatinine clearance is < 70 ml/min.

CONTRA-INDICATIONS

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

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

In accordance with current clinical clinical practice, if Keppra has to be discontinued it is recommended-to withdraw it gradually (e.g.. 500 mg twice daily decrements every two to four weeks). There are insufficient data for the withdrawal of concomitant antiepileptic medicinal products, once seizure control with Levetiracetam in the add-on situation has been reached, in order to reach monotherapy on Levetiracetam.
An increase in seizure frequency of more than 25/'0 has been reported in 14 and 26% of the L evetiracetam and placebo treated patients treated patients, respectively.
The administration of Keppra to patients with renal impairment may require dose adaption. In patients with severely impaired hepatic function, assessment of renal function is recommended before dose selection.

Pregnancy and lactation

There are no adequate data from the use of Keppra in pregnant woman. Studies in animals have shown reproductive toxicity. The potential risk for human is unknown. Keppra should not be used during pregnancy unless clearly necessary. Discontinuation of antiepileptic treatments may result in diseases worsening, harmful to the mother and the foetus.
Animal data show that Levetiracetam is excreted in breast milk. No data are available on the presence of Levetiracetam in human breast-feeding is not recommended.

Effects on ability to drive and use machine

No studies on the effects on the ability to drive and use machines have been, performed. Due to possible different individual sensitivity, some patients might experience, at the beginning of treatment or following a dose increase, somnolence or other central nervous system related symptoms. Therefore, caution is recommended in those patients when performing skilled tasks, e.g. driving vehicles or operating machinery.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Data indicate that Keppra did not influence the serum concentration of existing antiepileptic medicinal products (phenytoin, carbamazepin„ valproic acid, Phenobarbital, lamotrigine, gabapentin and primidone) and that these antiepileptic medicinal products did not influence the pharmacokinetics of Keppra.

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 drugs 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 the Levetiracetam on other actively secreted drugs, e. g. NSAIDs, sulfonamides and methotrexate is unknown.

Levetiracetam 1,000 mg daily did not influence the pharmacokinetics of oral contraceptives (ethynyl-estradiol and tevonorgestrel); 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-admin:stration 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.

UNDESIRABLE EFFECTS

Keppra has been administered 'to more than 3,000 subjects and patieo ts. A total of 1,023 patients with epilepsy participated in controlled clinical studies, Pooled safety data from these studies showed that 46.4 % and 42.2 % of the patients experienced undesirable effects in the Keppra and, respectively, and that 2.4 % and 2.0 % of the patients experienced serious undesirable effects in the Keppra and placebo groups, respectively.

The most commonly reported undesirable effects are 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.

Incidence of undesirable effects considered at least possibly related to Keppra by the investigator, from controlled clinical studies involving 1,023 epileptic patients (672 patients were treated with Keppra and 351 patients with piacebo) are: .

<u>Very common undesirable effects (> 10 %)</u>

- Body as a whole: asthenia
- Nervous system: somnolence

Common undesirable effects (> I % a 10 %)

- Body as a whole: accidental injury, headache
- Digestive system: anorexia, diarrhoea, dyspepsia, nausea
- Nervous system: amnesia, ataxia, convulsion, depression, dizziness, emotional [ability, hostility, insomnia, nervousness, tremor, vertigo
- Skin and appendages: rash
- Special senses: diplopia

OVERDOSE
There is no experience with doses greater than 5,000 mg/day.
No serious adverse events were reported by healthy volunteers after single doses of up to and including 5,000 mg.

b) Management of overdose
After an acute overdose, the stomach may be emptied by gastric lavage or by induction of emesia.
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.

STORAGE CONDITIONS AND EXPIRY DATE
Do not store over 30'C.
Don't use after the expiry date stated on the carton box and blister.

PRESENTATION
Keppra 250 mg: Box, 3 aluminium blisters, @ 10 film coated tablet
Keppra 500 mg: Box, 2 aluminium blisters, @ 10 film coated tablet
Keppra 1000 mg: Box, 2 aluminium blisters, @ 10 film coated tablet

Reg. No.:
Keppra 250 mg :
Keppra 500 mg :
Keppra 1000 mg:
Harus dengan resep dokter

Manufactured by:
UCB,Pharma S.A.,, Braine - l'Alleud, Belgium

Imported by:
PT. Darya-Varia Laboratoria Bogor - Indonesia.

Marketed by:
UCB Pharma, A Division of PT DVL
Jakarta -- Indonesia