KEPPRA

Levetiracetam

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

Levetiracetam, 250 mg, film-coated tablet
Each film-coated tablet contains 250 mg of levetiracetam.

Levetiracetam, 500 mg, film-coated tablet
Each film-coated tablet contains 500 mg of levetiracetam.

2. PHARMACEUTICAL FORM

Levetiracetam, 250 mg, film-coated tablet
Blue, oblong film-coated tablet scored and debossed with the code ucb and 250 on one side.
The score lines is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Levetiracetam, 500 mg, film-coated tablet
Yellow, oblong film-coated tablet scored and debossed with the code ucb and 500 on one side.
The score lines is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

3. CLINICAL INFORMATION

3.1 Indications

Levetiracetam is indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in patients with epilepsy.

3.2 Dosage and Administration

The film-coated tablets must be taken orally, swallowed with a sufficient quantity of liquid and may be taken with or without food. After oral administration the bitter taste of levetiracetam may be experienced. 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 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 (65 Years and Older)

Adjustment of the dose is recommended in elderly patients with compromised renal function.

Children

There are insufficient data to recommend the use of levetiracetam in children and adolescents under 16 years of age.

Renal Impairment

The daily dose must be individualised according to renal function. Refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in mL/min is needed. The CLcr in mL/min may be estimated from serum creatinine (mg/dL) determination using the following formula:

$$\text{CLcr (mL/min)} = \frac{[140\text{-age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \text{ (x0.85 for women)}$$

Dosing Adjustment 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 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.

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.

3.3. Contraindications
Levetiracetam is contraindicated in hypersensitivity to the active substance or other pyrrolidone derivates or to any of the excipients.

3.4. Warnings and Precautions
Discontinuation
If levetiracetam has to be discontinued it is recommended to withdraw it gradually (e.g. in adults and adolescents weighing more than 50 kg: 500 mg decreases twice daily 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% has been reported in 14 and 26% of the levetiracetam and placebo treated patients, respectively.

Renal or Hepatic Impairment
The administration of levetiracetam 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 Dosage and Administration*).

Acute Kidney Injury
The use of levetiracetam has been very rarely associated with acute kidney injury, with a time to onset ranging from a few days to several months.

Blood Cell Counts
Rare cases of decreased blood cell counts (neutropenia, agranulocytosis, leucopenia, thrombocytopenia and pancytopenia) have been described in association with levetiracetam administration, generally at the beginning of the treatment. Complete blood cell counts are advised in patients experiencing important weakness, pyrexia, recurrent infections or coagulation disorders (*see Section Adverse Reactions*).

Depression and/or Suicidal Ideation

Suicide, suicide attempt, suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents (including levetiracetam). A meta-analysis of randomized placebo-controlled trials of antiepileptic medicinal products has shown a small increased risk of suicidal thoughts and behaviour. The mechanism of this risk is not known.

Therefore, patients should be monitored for signs of depression and/or suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of depression and/or suicidal ideation or behaviour emerge.

Abnormal and Aggressive Behaviours
Levetiracetam may cause psychotic symptoms and behavioural abnormalities including irritability and aggressiveness. Patients treated with levetiracetam should be monitored for developing psychiatric signs suggesting important mood and/or personality changes. If such behaviours are noticed, treatment adaptation or gradual discontinuation should be considered. If discontinuation is considered, please see Section Discontinuation in Warnings and Precautions.

3.5. Interactions
Antiepileptic Medicinal Products
Pre-marketing data from clinical studies conducted in adults indicate that levetiracetam 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 levetiracetam.

Probenecid
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.

Methotrexate
Concomitant administration of levetiracetam and methotrexate has been reported to decrease methotrexate clearance, resulting in increased/prolonged blood methotrexate concentration to potentially toxic levels. Blood methotrexate and levetiracetam levels should be carefully monitored in patients treated concomitantly with the two drugs.

Oral Contraceptives, Digoxin and Warfarin
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.

Laxatives
There have been isolated reports of decreased levetiracetam efficacy when the osmotic laxative macrogol has been concomitantly administered with oral levetiracetam. Therefore, macrogol should not be taken orally for one hour before and for one hour after taking levetiracetam.

Food and Alcohol
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.

3. 6 Pregnancy and Lactation

Fertility

No impact on fertility was detected in animal studies. No clinical data are available, potential risk for human is unknown.

Pregnancy

Levetiracetam is not recommended during pregnancy and in women of childbearing potential not using contraception unless clearly necessary.

There are no adequate data available from the use of levetiracetam in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for human is unknown.

As with other antiepileptic medicinal products, physiological changes during pregnancy may affect levetiracetam concentration. Decrease in levetiracetam plasma concentrations has been observed during pregnancy. This decrease is more pronounced during the third trimester (up to 60% of baseline concentration before pregnancy). Appropriate clinical management of pregnant women treated with levetiracetam should be ensured. Discontinuation of antiepileptic treatments may result in exacerbation of the disease which could be harmful to be mother and the foetus.

Lactation

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

However, if levetiracetam treatment is needed during breastfeeding, the benefit/risk of the treatment should be weighed considering the importance of breastfeeding.

3.7 Ability to Perform Tasks That Require Judgment, Motor or Cognitive Skills

Levetiracetam has minor or moderate influence on the ability to drive and use machines. 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.

3.8 Adverse Reactions

Clinical Trial Data and Post-marketing Data

- **Summary of the safety profile**

  The adverse event profile presented below is based on the analysis of pooled placebo-controlled clinical trials with all indications studied, with a total of 3,416 patients treated with levetiracetam. These data are supplemented with the use of levetiracetam in corresponding open-label extension studies, as well as post-marketing experience. The most frequently reported adverse reactions were nasopharyngitis, somnolence, headache, fatigue and dizziness. The safety profile of levetiracetam is generally similar across age groups (adult and paediatric patients) and across the approved epilepsy indications.

  Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency. Frequencies are defined as:

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1,000 to <1/100
Rare	≥1/10,000 to <1/1,000
Very rare	<1/10,000

Not known (cannot be estimated from the available data).

Infections and infestations
Very common : nasopharyngitis
Rare : infection

Blood and lymphatic system disorders
Uncommon : thrombocytopenia, leukopenia
Rare : pancytopenia, neutropenia, agranulocytosis

Immune system disorders
Rare : drug reaction with eosinophilia and systemic symptoms (DRESS), hypersensitivity (including angioedema and anaphylaxis)

Metabolism and nutrition disorders
Common : anorexia
Uncommon : weight decreased, weight increase
Rare : hyponatraemia

Psychiatric disorders
Common : depression, hostility/aggression, anxiety, insomnia, nervousness/irritability
Uncommon : suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusional state, panic attack, affect lability/mood swings, agitation
Rare : completed suicide, personality disorder, thinking abnormal, delirium

Nervous system disorders
Very common : somnolence, headache
Common : convulsion, balance disorder, dizziness, lethargy, tremor
Uncommon : amnesia, memory impairment, coordination abnormal/ataxia, paraesthesia, disturbance in attention
Rare : choreoathetosis, dyskinesia, hyperkinesia, gait disturbance, encephalopathy

Eye disorders
Uncommon : diplopia, vision blurred

Ear and labyrinth disorders
Common : vertigo

Respiratory, thoracic and mediastinal disorders
Common : cough

Gastrointestinal disorders
Common : abdominal pain, diarrhoea, dyspepsia, vomiting, nausea
Rare : pancreatitis

Hepatobiliary disorders
Uncommon : liver function test abnormal
Rare : hepatic failure, hepatitis

Renal and urinary disorders
Rare : acute kidney injury

Skin and subcutaneous tissue disorders
Common : rash
Uncommon : alopecia, eczema, pruritus
Rare : toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme

Musculoskeletal and connective tissue disorders
Uncommon : muscular weakness, myalgia
Rare : rhabdomyolysis and blood creatine phosphokinase increased*

General disorders and administration site conditions
Common : asthenia/fatigue

Injury, poisoning and procedural complications
Uncommon : injury

* Prevalence is significantly higher in Japanese patients when compared to non-Japanese patients.

Description of selected adverse reactions
The risk of anorexia is higher when levetiracetam is co-administered with topiramate.

In several cases of alopecia, recovery was observed when levetiracetam was discontinued.

Bone marrow suppression was identified in some of the cases of pancytopenia.

Case of encephalopathy generally occurred at the beginning of the treatment (few days to a few months) and were reversible after treatment discontinuation.

3.9 Overdosage
Symptoms and Signs
Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with levetiracetam overdoses.

Treatment
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.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

3.10 Clinical Pharmacology
Pharmacodynamics
- **Pharmacotherapeutic group**
  Antiepileptics; other antiepileptics.

- **ATC code**
  N03AX14.

- **Mechanism of action**
  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.

  The mechanism of action of levetiracetam still remains to be fully elucidated.

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 analogs 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 medicinal product.

- **Pharmacodynamic effects**
  Levetiracetam induces seizure protection in a broad range of animal models of partial and primary 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 pharmacological profile of levetiracetam.

Pharmacokinetics
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).

The pharmacokinetic profile has been characterized following oral administration. A single dose of 1,500 mg levetiracetam diluted in 100 mL of a compatible diluent and infused intravenously over 15 minutes is bioequivalent to 1,500 mg levetiracetam oral intake, given as three 500 mg tablets.

- **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.

- **Metabolism**
  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 only for 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, 2C9, 2C19, 2D6, 2E1 and 1A2), glucuronyl transferase (UGT1A1 and UGT1A6) and epoxide hydroxylase activities. In addition, levetiracetam does not affect the *in vitro* glucuronidation of valproic acid.

  In human hepatocytes in culture, levetiracetam had little or no effect on CYP1A2, SULT1E1 or UGT1A1. Levetiracetam caused mild induction of CYP2B6 and CYP3A4. The *in vitro* data and *in vivo* interaction data on oral contraceptives, digoxin and warfarin indicate that no significant enzyme induction is expected *in vivo*. Therefore, the interaction of levetiracetam 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.

- **Special patient populations**
  Children (6 to 12 years)

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

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.

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 levetiracetam, based on creatinine clearance in patients with moderate and severe renal impairment.

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.

Clinical Studies
Not relevant for this product.

4. NON-CLINICAL INFORMATION
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenicity.

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.

No adverse effects on male or female fertility or reproduction performance were observed in rats at doses up to 1,800 mg/kg/day (x 6 the MRHD on a mg/m^2 or exposure basis) in parents and F1 generation.

Two embryo-foetal development (EFD) studies were performed in rats at 400, 1,200 and 3,600 mg/kg/day. At 3,600 mg/kg/day, in only one of the 2 EFD studies, there was a slight decrease in foetal weight associated with a marginal increase in skeletal variations/minor anomalies. There was no effect on embryo mortality and no increased incidence of malformations. The NOAEL (No Observed Adverse Effect Level) was 3,600 mg/kg/day for pregnant female rats (x 12 the MRHD on a mg/m^2 basis) and 1,200 mg/kg/day for foetuses.

Four embryo-foetal development studies were performed in rabbits covering doses of 200, 600, 800, 1,200 and 1,800 mg/kg/day. The dose level of 1,800 mg/kg/day induced a marked maternal toxicity and a decrease in foetal weight associated with increased incidence of foetuses with cardiovascular/skeletal anomalies. The NOAEL was <200 mg/kg/day for the dams and 200 mg/kg/day for the foetuses (equal to the MRHD on a mg/m^2 basis).

A peri- and post-natal development study was performed in rats with levetiracetam doses of 70, 350 and 1,800 mg/kg/day. The NOAEL was ≥1,800 mg/kg/day for the F0 females, and for the survival, growth and development of the F1 offspring up to weaning (x 6 the MRHD on a mg/m^2 basis).

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 (x 6-17 the MRHD on a mg/m^2 basis).

5. PHARMACEUTICAL INFORMATION

5.1 List of Excipients

Levetiracetam, 250 mg, film coated tablet
Sodium croscarmellose, macrogol 6000, colloidal anhydrous silica, magnesium stearate, opadry 85F20694 blue: polivinyl alcohol, titanium dioxide (E171), macrogol/PEG 3350, talc, FD&C blue #2/indigo carmine aluminium lake (E132).

Levetiracetam, 500 mg, film coated tablet
Sodium croscarmellose, macrogol 6000, colloidal anhydrous silica, magnesium stearate, opadry 85F32004 yellow: polivinyl alcohol, titanium dioxide (E171), macrogol/PEG 3350, talc, iron oxide yellow (E172).

5.2 Shelf Life

The expiry date is indicated on the packaging.

5.3 Storage

Store below 30°C.

5.4 Nature and Contents of Container

Thermoformed PVC/Aluminium blister strips.

5.5 Presentation

KEPPRA 250 mg, Box, 3 blisters @ 10 film-coated tablets, Reg. No DKI1083901017A1
KEPPRA 500 mg, Box, 2 blisters @ 10 film-coated tablets, Reg. No DKI1083901017B1

HARUS DENGAN RESEP DOKTER

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

Imported by
PT Glaxo Wellcome Indonesia
Jakarta, Indonesia

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