# 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:

$$\text{CLcr (mL/min)} = \frac{[140\text{-age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \; (\times 0.85 \text{ for women})$$

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 derivatives 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 randomised 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*.

**Worsening of Seizures**
As with other types of antiepileptic drugs, levetiracetam may rarely exacerbate seizure frequency or severity. This paradoxical effect was mostly reported within the first month after levetiracetam initiation or increase of the dose and was reversible upon drug discontinuation or dose decrease. Patients should be advised to consult their physician immediately in case of aggravation of epilepsy. Lack of efficacy or seizure worsening has for example been reported in patients with epilepsy associated with sodium voltage-gated channel alpha subunit 8 (SCN8A) mutations.

**Electrocardiogram QT Interval Prolongation**
Rare cases of ECG QT interval prolongation have been observed during the post-marketing surveillance. Levetiracetam should be used with caution in patients with QTc-interval prolongation, in patients concomitantly treated with drugs affecting the QTc-interval, or in patients with relevant pre-existing cardiac disease or electrolyte disturbances.

**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.

**Women of Childbearing Potential**
Specialist advice should be given to women who are of childbearing potential. Treatment with levetiracetam should be reviewed when a woman is planning to become pregnant. As with all antiepileptic medicines, sudden discontinuation of levetiracetam should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child. Monotherapy should be preferred whenever possible because therapy with multiple antiepileptic medicines AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated antiepileptics.

**Pregnancy**
Levetiracetam can be used during pregnancy, if after careful assessment it is considered clinically needed. In such case, the lowest effective dose is recommended.

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.

**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
Very rare : obsessive-compulsive disorder**

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, seizures aggravated, neuroleptic malignant syndrome*

Eye disorders
Uncommon : diplopia, vision blurred

Ear and labyrinth disorders
Common : vertigo

Cardiac disorders
Rare : electrocardiogram QT prolonged

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.
**Very rare cases of development of obsessive-compulsive disorders (OCD) in patients with underlying history of OCD or psychiatric disorders have been observed in post-marketing surveillance.

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.

Adverse events should be reported to GSK Indonesia via website https://gsk.public.reportum.com and Pusat Farmakovigilans/MESO Nasional Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif Badan Pengawas Obat dan Makanan. Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560

Email: pv-center@pom.go.id
Phone: +62-21-4244691 Ext.1079
Website: https://e-meso.pom.go.id/ADR

### 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 antiseizure 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 characterised 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 $P_{450}$ 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 $P_{450}$ 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

| | |
|---|---|
| Version number | : 01 |
| Reference | : NCDS version 12 |
| Date of local revision | : 6 October 2025 |

**INFORMASI UNTUK PASIEN**

# Keppra 250 mg & 500 mg Tablet Salut Selaput
# Levetiracetam

**Baca keseluruhan brosur ini secara teliti sebelum Anda mulai menggunakan obat ini.**
- Simpan brosur ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan pada dokter atau apoteker.
- Obat ini hanya diresepkan untuk Anda atau anak Anda. Jangan diberikan kepada orang lain. Hal tersebut dapat membahayakan mereka, meskipun gejala penyakit mereka sama dengan gejala Anda.
- Jika ada efek samping yang serius, atau jika Anda merasakan efek samping lain yang tidak tertulis dalam brosur ini, konsultasikan dengan dokter atau apoteker.

**Apa saja yang ada dalam brosur ini:**


## 1. Apa itu KEPPRA dan digunakan untuk apa

KEPPRA mengandung bahan aktif levetiracetam. Obat antiepilepsi yang digunakan untuk mengobati kejang pada epilepsi.

KEPPRA diindikasikan sebagai terapi tambahan dalam pengobatan kejang onset parsial dengan atau tanpa generalisasi sekunder pada pasien epilepsi.

## 2. Apa yang perlu Anda ketahui sebelum menggunakan KEPPRA

Jangan gunakan KEPPRA jika Anda **alergi** (hipersensitif) terhadap levetiracetam atau salah satu bahan lain dari obat ini (*Lihat bagian 6*).
➔ Jika ini terjadi pada Anda, **jangan gunakan** KEPPRA sampai Anda diperiksa oleh dokter Anda.

**Perhatian dalam menggunakan KEPPRA**
Sebelum menggunakan KEPPRA, dokter Anda perlu tahu:
- Jika Anda memiliki **masalah ginjal atau penyakit hati yang parah**, dokter Anda mungkin perlu menyesuaikan dosis KEPPRA Anda.
- Jika Anda sedang **hamil atau menyusui**, Anda mungkin hamil atau berencana untuk memiliki bayi (*Lihat bagian 2 – kehamilan dan menyusui*).
- Jika Anda sedang **mengonsumsi obat lain**.
- Jika Anda berusia **di atas 65 tahun**.
- Jika Anda memiliki riwayat keluarga atau kesehatan penyakit jantung, misalnya gangguan pada ritme jantung (terlihat pada elektrokardiogram) atau jika Anda sedang minum obat lain yang membuat Anda rentan mengalami gangguan ritme jantung atau jumlah garam yang tidak biasa di dalam tubuh.

➔ Periksakan kepada dokter Anda, jika Anda merasa mengalami salah satunya. Dokter Anda akan memutuskan apakah KEPPRA cocok untuk Anda.

KEPPRA tidak diindikasikan untuk anak-anak dan remaja di bawah 16 tahun (*Lihat bagian 1 – Apa itu KEPPRA dan digunakan untuk apa*).

**Saat Anda menggunakan KEPPRA**
- Jika Anda melihat adanya perlambatan dalam pertumbuhan atau perkembangan pubertas anak Anda yang tidak terduga, **hubungi dokter Anda**.
- Sebagian kecil orang yang dirawat dengan antiepilepsi seperti KEPPRA pernah memiliki **pikiran untuk menyakiti atau membunuh diri sendiri**. Jika suatu saat Anda memiliki pemikiran ini, **segera hubungi dokter Anda**.

- Jika Anda melihat adanya perilaku tidak normal dan agresif, atau jika Anda atau keluarga dan teman Anda melihat perubahan penting dalam *mood* atau perilaku, segera hubungi dokter Anda.
- Kejang Anda mungkin jarang menjadi lebih buruk atau lebih sering terjadi, terutama selama bulan pertama setelah memulai pengobatan atau meningkatkan dosis KEPPRA. Jika Anda perhatikan salah satu gejala ini saat menggunakan KEPPRA, segera hubungi dokter. Dalam bentuk epilepsi-onset-cepat yang sangat jarang terjadi (epilepsi yang dikaitkan dengan mutasi SCN8A) yang menyebabkan berbagai jenis kejang dan kehilangan ketrampilan, Anda mungkin menyadari bahwa kejang tetap muncul atau menjadi lebih buruk selama mengonsumsi obat ini.

**Kondisi yang perlu Anda perhatikan**
KEPPRA dapat memperburuk beberapa kondisi yang ada, atau menyebabkan efek samping yang serius seperti **reaksi alergi yang parah, reaksi kulit yang serius, *Drug Reaction with Eosinophilia and Systemic Symptoms* (DRESS), penurunan fungsi ginjal secara tiba-tiba, *encephalopathy*** (penyakit degeneratif otak), **depresi atau pikiran untuk bunuh diri**. Anda harus memperhatikan gejala tertentu saat Anda menggunakan KEPPRA untuk mengurangi risiko kejadian di atas. *Lihat Efek samping yang mungkin terjadi – bagian 4*.

**Obat-obatan lain dan KEPPRA**
**Beritahu dokter atau apoteker jika Anda sedang menggunakan obat lain,** jika Anda baru saja menggunakannya, atau mulai menggunakan yang baru. Termasuk obat-obatan yang dibeli tanpa resep dokter. Jangan minum **macrogol** (obat yang digunakan sebagai **pencahar**) selama satu jam sebelum dan satu jam setelah menggunakan KEPPRA karena ini dapat menyebabkan kehilangan efeknya. Anda akan diawasi secara ketat jika Anda menggunakan KEPPRA dengan:
- Methotrexate (digunakan untuk mengobati jenis **kanker** tertentu).

Beberapa obat lain dapat mempengaruhi cara kerja KEPPRA, atau mungkin menyebabkan efek samping. KEPPRA juga dapat mempengaruhi cara kerja beberapa obat lain, termasuk:
- Probenecid (digunakan untuk mengobati **asam urat**).

➔ **Beritahu dokter Anda atau apoteker Anda jika Anda menggunakan obat tersebut.**

**Kehamilan dan menyusui**
**KEPPRA tidak disarankan untuk digunakan selama kehamilan.**
- **Beritahu dokter Anda jika Anda sedang hamil** atau berencana untuk hamil.
- Gunakan **kontrasepsi** saat Anda menggunakan KEPPRA untuk mencegah kehamilan.
- **Jika Anda hamil selama pengobatan** dengan KEPPRA, beritahu dokter Anda.

KEPPRA dapat digunakan selama kehamilan, hanya jika setelah penilaian yang cermat dianggap perlu oleh dokter Anda. Anda tidak boleh menghentikan pengobatan Anda tanpa diskusi dengan dokter Anda. Risiko cacat lahir selama anak Anda belum lahir tidak dapat diabaikan. KEPPRA menunjukkan efek reproduksi yang tidak diinginkan pada studi hewan.

**Menyusui tidak disarankan** selama pengobatan dengan KEPPRA. Bahan aktif KEPPRA dapat masuk ke dalam ASI. Diskusikan dengan dokter Anda tentang ini.

**Mengemudi dan menggunakan mesin**
**KEPPRA dapat membuat Anda merasa mengantuk** dan memiliki efek samping lain yang membuat Anda kurang waspada. Hal ini lebih mungkin terjadi pada awal pengobatan atau setelah peningkatan dosis.

➔ **Jangan mengemudi atau menggunakan mesin** kecuali Anda yakin Anda tidak terpengaruh.

## 3. Cara menggunakan KEPPRA

**Berapa banyak yang harus digunakan**
**Selalu gunakan KEPPRA secara tepat sesuai saran dokter Anda.** Konsultasikan dengan dokter, perawat atau apoteker jika Anda tidak yakin.

KEPPRA harus diminum **dua kali sehari**, sekali di pagi hari dan sekali di malam hari, pada waktu yang sama setiap hari.

**Terapi tambahan**
**Dewasa dan remaja di atas 16 tahun**
**Dosis awal KEPPRA adalah 500 mg dua kali sehari**. Dokter Anda mungkin memutuskan untuk secara bertahap meningkatkan dosis Anda hingga maksimum **1.500 mg, dua kali sehari** tergantung bagaimana Anda merespons obat ini.

**Pasien dengan masalah ginjal**
Dokter Anda akan memutuskan dosis KEPPRA yang benar untuk Anda/anak Anda tergantung pada fungsi ginjal dan berat badan.

**Bagaimana cara menggunakan KEPPRA**
Telan tablet KEPPRA dengan air yang cukup. Anda dapat mengonsumsi KEPPRA dengan atau tanpa makanan. Setelah pemberian oral, rasa pahit levetiracetam mungkin terasa.

**Apabila Anda lupa menggunakan KEPPRA**
**Jangan menggunakan KEPPRA berlebih untuk menggantikan dosis yang terlewatkan. Hubungi dokter Anda jika lupa menggunakan satu dosis atau lebih.**

**Apabila Anda menggunakan terlalu banyak KEPPRA**
Jika Anda menggunakan KEPPRA lebih dari yang seharusnya, Anda mungkin **merasa lebih mengantuk, gelisah atau mengalami efek samping lainnya seperti penurunan kewaspadaan, agresif, pernafasan pendek dan kehilangan kesadaran (koma).**
➔ **Jangan tunda. Segera hubungi dokter atau bagian gawat darurat rumah sakit terdekat.** Jika memungkinkan, tunjukkan kemasan KEPPRA ini.

**Jangan berhenti menggunakan KEPPRA tanpa saran dari dokter Anda**
**KEPPRA harus diminum selama dokter Anda merekomendasikannya**. Jangan berhenti kecuali dokter Anda menyarankan untuk berhenti. Jika Anda menderita epilepsi, menghentikan penggunaan obat secara tiba-tiba dapat meningkatkan kejang yang Anda alami.
Untuk menghentikan pengobatan, KEPPRA harus dihentikan secara bertahap. Dokter Anda akan menginstruksikan kepada Anda mengenai penghentian KEPPRA secara bertahap.
➔ Tanyakan kepada dokter atau apoteker Anda jika Anda memiliki pertanyaan tentang penggunaan produk ini.

## 4. Efek samping yang mungkin terjadi

Seperti semua obat-obatan, KEPPRA dapat menyebabkan efek samping, tetapi tidak semua orang mengalaminya.

**Kondisi yang perlu diwaspadai**
**Reaksi alergi yang parah.** Ini jarang terjadi pada orang yang menggunakan KEPPRA. Gejalanya meliputi:
- Timbul ruam dan gatal (urtikaria).
- Bengkak, kadang pada wajah atau mulut (*angioedema*), menyebabkan kesulitan bernafas.
- Pingsan atau kehilangan kesadaran.

**Reaksi kulit yang serius.** Ini jarang terjadi pada orang yang menggunakan KEPPRA. Gejalanya meliputi:
- Ruam kulit, yang mungkin melepuh, dan tampak seperti sasaran kecil (bintik-bintik hitam di tengah yang lebih pucat, dengan cincin gelap di sekitar tepi – *erythema multiforme*).
- Ruam yang meluas dengan lepuh dan kulit yang mengelupas, terutama di sekitar mulut, hidung, mata dan alat kelamin (*Stevens Johnson Syndrome*).
- Pengelupasan kulit yang ekstensif di sebagian besar permukaan tubuh (*toxic epidermal necrolysis*).

**Reaksi obat dengan *Eosinofilia* dan *Systemic Symptoms* (DRESS).** Ini jarang terjadi pada orang yang menggunakan KEPPRA. Gejalanya meliputi:

- Gejala mirip flu dan timbul ruam pada wajah yang diikuti dengan ruam yang berkepanjangan dengan suhu tinggi.
- Pembesaran kelenjar getah bening.
- Peningkatan kadar enzim hati yang terlihat pada tes darah dan peningkatan jenis sel darah putih (*eosinophilia*).

**Penurunan fungsi ginjal secara tiba-tiba.** Ini jarang terjadi pada orang yang menggunakan KEPPRA. Gejalanya meliputi:
- Volume urin rendah.
- Kelelahan, mual, muntah.
- Kebingungan.
- Bengkak di tungkai, pergelangan kaki atau kaki.

***Encephalopathy* (penyakit degeneratif otak).** Ini biasanya terjadi di awal pengobatan (beberapa hari sampai beberapa bulan) pada orang yang menggunakan KEPPRA. Gejalanya meliputi:
- Perubahan mental yang serius atau tanda-tanda kebingungan.
- Merasa mengantuk.
- Hilang ingatan (amnesia), gangguan ingatan (sering lupa).
- Perilaku abnormal.
- Tanda-tanda neurologis lainnya termasuk gerakan yang tidak disengaja atau tidak terkontrol.

**Depresi.** Ini biasa terjadi pada orang yang menggunakan KEPPRA.

**Pikiran untuk bunuh diri.** Ini jarang terjadi pada orang yang menggunakan KEPPRA.

➔ Dapatkan segera bantuan medis jika Anda mengalami gejala-gejala ini.

**Efek samping yang sangat umum** (terjadi hingga lebih dari **1 dari 10** orang)
- Radang nasofaring (nasofaringitis).
- Merasa mengantuk.
- Sakit kepala.

**Efek samping yang umum** (terjadi pada hingga **1 dari 10** orang)
- Kehilangan nafsu makan (anoreksia) – terutama jika Anda menggunakan obat lain yang disebut topiramate.
- Depresi, agresif, kecemasan, sulit tidur, gugup atau mudah tersinggung.
- Kejang, gangguan keseimbangan, pusing, kantuk yang abnormal (lesu), tremor.
- Sensasi berputar (vertigo).
- Batuk.
- Sakit perut, diare, gangguan pencernaan, muntah, rasa mual (mual).
- Ruam.
- Merasa lemah atau kekurangan energi.

**Efek samping yang tidak umum** (terjadi pada hingga **1 dari 100** orang)
- Berat badan menurun atau bertambah.
- Percobaan bunuh diri dan keinginan untuk bunuh diri, gangguan mental, perilaku abnormal, melihat atau mendengar sesuatu yang tidak benar-benar ada (halusinasi), marah, bingung, serangan panik, ketidakstabilan emosi/suasana hati, agitasi.
- Hilang ingatan, gangguan ingatan (sering lupa), koordinasi abnormal atau kehilangan koordinasi gerakan tubuh, kesemutan atau mati rasa pada tangan atau kaki, gangguan perhatian (kehilangan konsentrasi).
- Penglihatan ganda, penglihatan kabur.
- Rambut rontok atau menipis yang tidak biasa, eksim, gatal.
- Kelemahan otot, nyeri otot.
- Cedera.

Efek samping yang tidak umum yang mungkin muncul dalam tes darah:
- Penurunan jumlah trombosit darah – sel yang membantu darah membeku (trombositopenia).
- Penurunan jumlah sel darah putih (leukopenia).
- Nilai tinggi/abnormal pada tes fungsi hati.

**Efek samping yang jarang terjadi** (terjadi pada hingga **1 dari 1.000** orang)
- Infeksi.
- Reaksi alergi (*lihat Reaksi alergi yang parah di awal bagian 4*).
- Reaksi hipersensitivitas yang diinduksi obat yang meliputi demam, ruam, dan kelainan darah (*lihat Reaksi obat dengan Eosinophilia dan Systemic Symptoms (DRESS) di awal bagian 4*).
- Bunuh diri, gangguan kepribadian (masalah perilaku), pemikiran abnormal, kebingungan parah (delirium).
- Kejang otot tak terkendali mempengaruhi mata, kepala, leher dan tubuh, gerakan tak terkendali, hiperaktif (terlalu aktif).
- *Encephalopathy* (penyakit degeneratif otak) (*lihat encephalopathy di awal bagian 4*).
- Kejang bisa menjadi lebih buruk atau lebih sering terjadi.
- Gangguan pada irama jantung (elektrokardiogram).
- Radang pankreas.
- Gagal hati, radang hati.
- *Erythema multiforme, Stevens Johnson Syndrome, toxic epidermal necrolysis* (*lihat Reaksi kulit yang serius di awal bagian 4*).
- Cedera ginjal akut (*lihat Penurunan fungsi ginjal secara tiba-tiba di awal bagian 4*).
- *Rhabdomyolysis* (kerusakan jaringan otot) dan peningkatan kreatin fosfokinase darah. Prevalensi secara signifikan lebih tinggi pada pasien Jepang jika dibandingkan dengan pasien non-Jepang.
- Pincang atau kesulitan berjalan.
- Kombinasi demam, kaku otot, tekanan darah dan detak jantung tidak stabil, kebingungan, kesadaran rendah (kemungkinan gejala gangguan yang disebut *neuroleptic malignant syndrome*). Prevalensi secara signifikan lebih tinggi pada pasien Jepang jika dibandingkan dengan pasien non-Jepang.

Efek samping jarang yang mungkin muncul dalam tes darah:
- Penurunan jumlah semua jenis sel darah.
- Penurunan natrium dalam darah.
- *Neutropenia*.
- *Agranulocytosis*.

**Efek samping yang sangat jarang** (terjadi pada hingga **1 dari 1,0000** orang)
- Pikiran yang tidak diinginkan muncul secara berulang atau sensasi atau keinginan untuk melakukan sesuatu secara berulang-ulang (*Obsessive-Compulsive Disorder*).

➔ Beritahu dokter atau apoteker Anda jika salah satu efek samping yang terdaftar menjadi parah, atau jika Anda melihat efek samping yang tidak tercantum dalam brosur ini.

**Pelaporan efek samping**
Jika efek samping menjadi serius, atau jika Anda melihat terdapat efek samping yang tidak tercantum dalam brosur ini, segera konsultasikan pada dokter atau apoteker Anda.

Laporkan Kejadian Tidak Diinginkan (KTD) ke GSK Indonesia melalui situs web https://gsk.public.reportum.com .

## 5. Bagaimana cara penyimpanan KEPPRA

Simpan obat ini jauh dari jangkauan anak-anak.

Jangan menggunakan obat setelah tanggal kedaluwarsa yang tertulis pada kemasan.

Simpan di bawah suhu 30˚C.

Jangan membuang obat apa pun di air limbah atau limbah rumah tangga. Tanyakan pada apoteker bagaimana membuang obat yang tidak digunakan lagi. Ini akan membantu melindungi lingkungan.

## 6. Isi dari kemasan dan informasi lain

**Kandungan pada tablet salut selaput KEPPRA**

- Bahan aktif levetiracetam.
- Tiap tablet salut selaput mengandung 250 mg atau 500 mg levetiracetam.
- Komponen lainnya adalah *croscarmellose sodium, macrogol 6000, silica coloidal anhydrous, magnesium stearate, opadry 85F20694* (250 mg), *opadry 85F32004* (500 mg).

**HARUS DENGAN RESEP DOKTER**

KEPPRA 250 mg, Dus, 3 blister @ 10 tablet salut selaput Reg. No. DKI1083901017A1
KEPPRA 500 mg, Dus, 2 blister @ 10 tablet salut selaput Reg. No. DKI1083901017B1

Diproduksi oleh:
UCB S.A. Pharma Sector
Braine – l'Alleud, Belgia

Diimpor oleh:
PT Glaxo Wellcome Indonesia
Jakarta, Indonesia.

*Version number : 01*
*Reference : NCDS version 12*
*Date of local revision : 6 October 2025*