ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT

Keppra 250 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 250 mg levetiracetam.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
Blue, oblong, scored and debossed with the code “ucb” and “250” on one side.

4. CLINICAL PARTICULARS

4.1 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.

4.2 Posology and method of administration

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

- 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 (65 years and older)
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:

<table>
<thead>
<tr>
<th>Weight</th>
<th>Starting dose: 10 mg/kg twice daily</th>
<th>Maximum dose: 30 mg/kg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 kg (1)</td>
<td>150 mg twice daily</td>
<td>450 mg twice daily</td>
</tr>
<tr>
<td>20 kg (1)</td>
<td>200 mg twice daily</td>
<td>600 mg twice daily</td>
</tr>
<tr>
<td>25 kg</td>
<td>250 mg twice daily</td>
<td>750 mg twice daily</td>
</tr>
<tr>
<td>From 50 kg (2)</td>
<td>500 mg twice daily</td>
<td>1500 mg twice daily</td>
</tr>
</tbody>
</table>

(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 (see section 5.2).

Patients with renal impairment

The daily dose must be individualised according to renal function.

For adult patients, refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in ml/min is needed. The CLcr in ml/min may be estimated from serum creatinine (mg/dl) determination using the following formula:

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

Then CLcr is adjusted for body surface area (BSA) as follows:

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

Dosing adjustment for adult patients with impaired renal function

<table>
<thead>
<tr>
<th>Group</th>
<th>Creatinine clearance (ml/min/1.73m^2)</th>
<th>Dosage and frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt; 80</td>
<td>500 to 1,500 mg twice daily</td>
</tr>
<tr>
<td>Mild</td>
<td>50-79</td>
<td>500 to 1,000 mg twice daily</td>
</tr>
<tr>
<td>Moderate</td>
<td>30-49</td>
<td>250 to 750 mg twice daily</td>
</tr>
</tbody>
</table>
### Severe End-stage renal disease patients

<table>
<thead>
<tr>
<th>Severe End-stage renal disease patients</th>
<th>250 to 500 mg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undergoing dialysis (1)</td>
<td>500 to 1,000 mg once daily (2)</td>
</tr>
</tbody>
</table>

(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.

### 4.3 Contraindications

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

### 4.4 Special warnings and special precautions for use

In accordance with current clinical practice, if Keppra has to be discontinued it is recommended to withdraw it gradually (e.g., in adults: 500 mg 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 section 4.2).

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.

### 4.5 Interaction with other medicinal products and other forms of interaction

Pre-marketing data from clinical studies conducted in adults indicate that Keppra did not influence the serum concentrations of existing antiepileptic medicinal products (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these antiepileptic medicinal products did not influence the pharmacokinetics of Keppra.

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.

### 4.6 Pregnancy and lactation

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

Levetiracetam is excreted in human breast milk. Therefore, breast-feeding 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.

### 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Due to possible different individual sensitivity, some patients might experience somnolence or other central nervous system related symptoms, 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.

### 4.8 Undesirable effects

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

In monotherapy 49.8% of the subjects experienced at least one drug related undesirable effect. The most frequently reported undesirable effects were fatigue and somnolence.

A study conducted in paediatric patients (4 to 16 years) with partial onset seizures showed that 55.4% of the patients in the Keppra group and 40.2% of the patients in the placebo group experienced undesirable effects. Serious undesirable effects were experienced in 0.0% of the patients in the Keppra group and 1.0% of the patients in the placebo group. The most commonly reported undesirable effects were somnolence, hostility, nervousness, emotional lability, agitation, anorexia, asthenia and headache in the paediatric population. Safety results in paediatric patients were consistent with the safety profile of levetiracetam in adults except for behavioural and psychiatric adverse events which were more common in children than in adults (38.6% versus 18.6%). However, the relative risk was similar in children as compared to adults.

A study conducted in adults and adolescents with myoclonic seizures (12 to 65 years) showed that 33.3% of the patients in the Keppra group and 30.0% of the patients in the placebo group experienced undesirable effects that were judged to be related to treatment. The most commonly reported undesirable effects were headache and somnolence. The incidence of undesirable effects in patients with myoclonic seizures was lower than that in adult patients with partial onset seizures (33.3% versus 46.4%).

A study conducted in adults and children (4 to 65 years) with idiopathic generalised epilepsy with primary generalised tonic-clonic seizures showed that 39.2% of the patients in the Keppra group and 29.8% of the patients in the placebo group experienced undesirable effects that were judged to be related to treatment. The most commonly reported undesirable effect was fatigue.

Undesirable effects reported in clinical studies (adults and children) or from post-marketing experience are listed in the following table per System Organ Class and per frequency. For clinical trials, the frequency is defined as follows: very common ($\geq 1/10$); common ($\geq 1/100, <1/10$); uncommon ($\geq 1/1,000, <1/100$); rare ($\geq 1/10,000, <1/1,000$); very rare ($<1/10,000$), including isolated reports. Data from post-marketing experience are insufficient to support an estimate of their incidence in the population to be treated.

- **General disorders and administration site conditions**
  - Very common: asthenia/fatigue

- **Nervous system disorders**
  - Very common: somnolence
  - Common: amnesia, ataxia, convulsion, dizziness, headache, hyperkinesia, tremor, balance disorder, disturbance in attention, memory impairment.
  - Post-marketing experience: paraesthesia

- **Psychiatric disorders**
  - Common: agitation, depression, emotional lability/mood swings, hostility/aggression, insomnia, nervousness/irritability, personality disorders, thinking abnormal
  - Post-marketing experience: abnormal behaviour, anger, anxiety, confusion, hallucination, psychotic disorder, suicide, suicide attempt and suicidal ideation

- **Gastrointestinal disorders**
  - Common: abdominal pain, diarrhoea, dyspepsia, nausea, vomiting
  - Post-marketing experience: pancreatitis
- Hepatobiliary disorders:
  Post-marketing experience: hepatic failure, hepatitis, liver function test abnormal

- Metabolism and nutrition disorders
  Common: anorexia, weight increase.
  The risk of anorexia is higher when topiramate is coadministered with levetiracetam.
  Post-marketing experience: weight loss

- Ear and labyrinth disorders
  Common: vertigo

- Eye disorders
  Common: diplopia, vision blurred

- Musculoskeletal and connective tissue disorders
  Common: myalgia

- Injury, poisoning and procedural complications
  Common: accidental injury

- Infections and infestations
  Common: infection, nasopharyngitis

- Respiratory, thoracic and mediastinal disorders
  Common: cough increased

- Skin and subcutaneous tissue disorders
  Common: rash, eczema, pruritus
  Post-marketing experience: alopecia: in several cases, recovery was observed when Keppra was discontinued.

- Blood and lymphatic system disorders
  Common: thrombocytopenia
  Post-marketing experience: leukopenia, neutropenia, pancytopenia (with bone marrow suppression identified in some of the cases)

4.9 Overdose

Symptoms

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

Management of overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
**Pharmacological group**: antiepileptics, ATC code: N03AX14.
The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances.

**Mechanism of action**

The mechanism of action of levetiracetam still remains to be fully elucidated but appears to be different from the mechanisms of current antiepileptic medicinal products. *In vitro* and *in vivo* experiments suggest that levetiracetam does not alter basic cell characteristics and normal neurotransmission. *In vitro* studies show that levetiracetam affects intraneuronal Ca2+ levels by partial inhibition of N-type Ca2+ currents and by reducing the release of Ca2+ 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.

**Clinical experience**

*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 adults, levetiracetam efficacy has been demonstrated in 3 double-blind, placebo-controlled studies at 1000 mg, 2000 mg, or 3000 mg/day, given in 2 divided doses, with a treatment duration of up to 18 weeks. In a pooled analysis, the percentage of patients who achieved 50% or greater reduction from baseline in the partial onset seizure frequency per week at stable dose (12/14 weeks) was of 27.7%, 31.6% and 41.3% for patients on 1000, 2000 or 3000 mg levetiracetam respectively and of 12.6% for patients on placebo.

In pediatric patients (4 to 16 years of age), levetiracetam efficacy was established in a double-blind, placebo-controlled study, which included 198 patients and had a treatment duration of 14 weeks. In this study, the patients received levetiracetam as a fixed dose of 60 mg/kg/day (with twice a day dosing). 44.6% of the levetiracetam treated patients and 19.6% of the patients on placebo had a 50% or greater reduction from baseline in the partial onset seizure frequency per week. With continued long-term treatment, 11.4% of the patients were seizure-free for at least 6 months and 7.2% were seizure-free for at least 1 year.

*Monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy.*

Efficacy of levetiracetam as monotherapy was established in a double-blind, parallel group, non-inferiority comparison to carbamazepine controlled release (CR) in 576 patients 16 years of age or
older with newly or recently diagnosed epilepsy. The patients had to present with unprovoked partial seizures or with generalized tonic-clonic seizures only. The patients were randomized to carbamazepine CR 400 – 1200 mg/day or levetiracetam 1000 - 3000 mg/day, the duration of the treatment was up to 121 weeks depending on the response. Six-month seizure freedom was achieved in 73.0% of levetiracetam-treated patients and 72.8% of carbamazepine-CR treated patients; the adjusted absolute difference between treatments was 0.2% (95% CI: -7.8 8.2). More than half of the subjects remained seizure free for 12 months (56.6% and 58.5% of subjects on levetiracetam and on carbamazepine CR respectively).

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

**Adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.**

Levetiracetam efficacy was established in a double-blind, placebo-controlled study of 16 weeks duration, in patients 12 years of age and older suffering from idiopathic generalized epilepsy with myoclonic seizures in different syndromes. The majority of patients presented with juvenile myoclonic epilepsy.

In this study, levetiracetam, dose was 3000 mg/day given in 2 divided doses.

58.3% of the levetiracetam treated patients and 23.3% of the patients on placebo had at least a 50% reduction in myoclonic seizure days per week. With continued long-term treatment, 28.6% of the patients were free of myoclonic seizures for at least 6 months and 21.0% were free of myoclonic seizures for at least 1 year.

**Adjunctive therapy in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalised epilepsy.**

Levetiracetam efficacy was established in a 24-week double-blind, placebo-controlled study which included adults, adolescents and a limited number of children suffering from idiopathic generalized epilepsy with primary generalized tonic-clonic (PGTC) seizures in different syndromes (juvenile myoclonic epilepsy, juvenile absence epilepsy, childhood absence epilepsy, or epilepsy with Grand Mal seizures on awakening). In this study, levetiracetam dose was 3000 mg/day for adults and adolescents or 60 mg/kg/day for children, given in 2 divided doses.

72.2% of the levetiracetam treated patients and 45.2% of the patients on placebo had a 50% or greater decrease in the frequency of PGTC seizures per week. With continued long-term treatment, 47.4% of the patients were free of tonic-clonic seizures for at least 6 months and 31.5% were free of tonic-clonic seizures for at least 1 year.

### 5.2 Pharmacokinetic properties

Levetiracetam is a highly soluble and permeable compound. The pharmacokinetic profile is linear with low intra- and inter-subject variability. There is no modification of the clearance after repeated administration. There is no evidence for any relevant gender, race or circadian variability. The pharmacokinetic profile is comparable in healthy volunteers and in patients with epilepsy.

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

A significant correlation between saliva and plasma concentrations has been shown in adults and children (ratio of saliva/plasma concentrations ranged from 1 to 1.7 for oral tablet formulation and after 4 hours post-dose for oral solution formulation).
Adults and adolescents

Absorption

Levetiracetam is rapidly absorbed after oral administration. Oral absolute bioavailability is close to 100%.
Peak plasma concentrations (C_max) are achieved at 1.3 hours after dosing. Steady-state is achieved after two days of a twice daily administration schedule.
Peak concentrations (C_max) are typically 31 and 43 µg/ml following a single 1,000 mg dose and repeated 1,000 mg twice daily dose, respectively.
The extent of absorption is dose-independent and is not altered by food.

Distribution

No tissue distribution data are available in humans.
Neither levetiracetam nor its primary metabolite are significantly bound to plasma proteins (< 10 %).
The volume of distribution of levetiracetam is approximately 0.5 to 0.7 l/kg, a value close to the total body water volume.

Biotransformation

Levetiracetam is not extensively metabolised in humans. The major metabolic pathway (24 % of the dose) is an enzymatic hydrolysis of the acetamide group. Production of the primary metabolite, ucb L057, is not supported by liver cytochrome P450 isoforms. Hydrolysis of the acetamide group was measurable in a large number of tissues including blood cells. The metabolite ucb L057 is pharmacologically inactive.

Two minor metabolites were also identified. One was obtained by hydroxylation of the pyrrolidone ring (1.6 % of the dose) and the other one by opening of the pyrrolidone ring (0.9 % of the dose). Other unidentified components accounted 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 Keppra with other substances, or vice versa, is unlikely.

Elimination

The plasma half-life in adults was 7±1 hours and did not vary either with dose, route of administration or repeated administration. The mean total body clearance was 0.96 ml/min/kg.

The major route of excretion was via urine, accounting for a mean 95 % of the dose (approximately 93 % of the dose was excreted within 48 hours). Excretion via faeces accounted for only 0.3 % of the dose.
The cumulative urinary excretion of levetiracetam and its primary metabolite accounted for 66 % and 24 % of the dose, respectively during the first 48 hours.
The renal clearance of levetiracetam and ucb L057 is 0.6 and 4.2 ml/min/kg respectively indicating that levetiracetam is excreted by glomerular filtration with subsequent tubular reabsorption and that the primary metabolite is also excreted by active tubular secretion in addition to glomerular filtration. Levetiracetam elimination is correlated to creatinine clearance.

**Elderly**

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

**Children (4 to 12 years)**

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

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

**Infants and children (1 month to 4 years)**

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

**Renal impairment**

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

In anuric end-stage renal disease adult subjects the half-life was approximately 25 and 3.1 hours during interdialytic and intradialytic periods, respectively. The fractional removal of levetiracetam was 51 % during a typical 4-hour dialysis session.

**Hepatic impairment**

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

**5.3 Preclinical safety data**

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.
In reproductive toxicity studies in the rat, levetiracetam induced developmental toxicity (increase in skeletal variations/minor anomalies, retarded growth, increased pup mortality) at exposure levels similar to or greater than the human exposure. In the rabbit foetal effects (embryonic death, increased skeletal anomalies, and increased malformations) were observed in the presence of maternal toxicity. The systemic exposure at the observed no effect level in the rabbit was about 4 to 5 times the human exposure.

Neonatal and juvenile animal studies in rats and dogs demonstrated that there were no adverse effects seen in any of the standard developmental or maturation endpoints at doses up to 1800 mg/kg/day corresponding to 30 times the maximum recommended human dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Sodium croscarmellose
Macrogol 6000
Colloidal anhydrous silica
Magnesium stearate

Film-coating Opadry 85F20694:
Polyvinyl alcohol-part. hydrolyzed
Titanium dioxide (E171)
Macrogol 3350
Talc
Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Keppra 250 mg film-coated tablets are packaged in aluminium/PVC blisters placed into cardboard boxes containing 20, 30, 50, 60, 100 and 200 film-coated tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

UCB Pharma S.A.
Allée de la Recherche 60
8. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/146/001  
EU/1/00/146/002  
EU/1/00/146/003  
EU/1/00/146/004  
EU/1/00/146/005  
EU/1/00/146/029

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 September 2000  
Date of last renewal: 08 July 2005

10. DATE OF REVISION OF THE TEXT
1. **NAME OF THE MEDICINAL PRODUCT**

Keppra 500 mg film-coated tablets.

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film-coated tablet contains 500 mg levetiracetam. 
For a full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Film-coated tablet.
Yellow, oblong, scored and debossed with the code “ucb” and “500” on one side.

4. **CLINICAL PARTICULARS**

4.1 **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.

4.2 **Posology and method of administration**

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

- **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 (65 years and older)**
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:**

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Starting dose: 10 mg/kg twice daily</th>
<th>Maximum dose: 30 mg/kg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 kg</td>
<td>150 mg twice daily</td>
<td>450 mg twice daily</td>
</tr>
<tr>
<td>20 kg</td>
<td>200 mg twice daily</td>
<td>600 mg twice daily</td>
</tr>
<tr>
<td>25 kg</td>
<td>250 mg twice daily</td>
<td>750 mg twice daily</td>
</tr>
<tr>
<td>From 50 kg</td>
<td>500 mg twice daily</td>
<td>1500 mg twice daily</td>
</tr>
</tbody>
</table>

(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 (see section 5.2).

**Patients with renal impairment**

The daily dose must be individualised according to renal function.

For adult patients, refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in ml/min is needed. The CLcr in ml/min may be estimated from serum creatinine (mg/dl) determination using the following formula:

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

Then CLcr is adjusted for body surface area (BSA) as follows:

\[
\text{CLcr (ml/min/1.73 m^2)} = \frac{\text{CLcr (ml/min)}}{\text{BSA subject (m^2)}} \times 1.73
\]

**Dosing adjustment for adult patients with impaired renal function**

<table>
<thead>
<tr>
<th>Group</th>
<th>Creatinine clearance (ml/min/1.73 m^2)</th>
<th>Dosage and frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt; 80</td>
<td>500 to 1,500 mg twice daily</td>
</tr>
<tr>
<td>Mild</td>
<td>50-79</td>
<td>500 to 1,000 mg twice daily</td>
</tr>
<tr>
<td>Moderate</td>
<td>30-49</td>
<td>250 to 750 mg twice daily</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt; 30</td>
<td>250 to 500 mg twice daily</td>
</tr>
</tbody>
</table>
End-stage renal disease patients undergoing dialysis (1)  
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.

4.3 Contraindications

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

4.4 Special warnings and special precautions for use

In accordance with current clinical practice, if Keppra has to be discontinued it is recommended to withdraw it gradually (e.g. in adults: 500 mg 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 section 4.2).

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.

4.5 Interaction with other medicinal products and other forms of interaction

Pre-marketing data from clinical studies conducted in adults indicate that Keppra did not influence the serum concentrations of existing antiepileptic medicinal products (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these antiepileptic medicinal products did not influence the pharmacokinetics of Keppra.

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-
estriadiol and levonorgestrel); endocrine parameters (luteinizing hormone and progesterone) were not
modified. Levetiracetam 2,000 mg daily did not influence the pharmacokinetics of digoxin and
warfarin; prothrombin times were not modified. Co-administration with digoxin, oral contraceptives
and warfarin did not influence the pharmacokinetics of levetiracetam.

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

The extent of absorption of levetiracetam was not altered by food, but the rate of absorption was
slightly reduced.
No data on the interaction of levetiracetam with alcohol are available.

4.6 Pregnancy and lactation

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

Levetiracetam is excreted in human breast milk. Therefore, breast-feeding 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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.
Due to possible different individual sensitivity, some patients might experience somnolence or other
central nervous system related symptoms, 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.

4.8 Undesirable effects

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

In monotherapy 49.8% of the subjects experienced at least one drug related undesirable effect. The most frequently reported undesirable effects were fatigue and somnolence.

A study conducted in paediatric patients (4 to 16 years) with partial onset seizures showed that 55.4% of the patients in the Keppra group and 40.2% of the patients in the placebo group experienced undesirable effects. Serious undesirable effects were experienced in 0.0% of the patients in the Keppra group and 1.0% of the patients in the placebo group. The most commonly reported undesirable effects were somnolence, hostility, nervousness, emotional lability, agitation, anorexia, asthenia and headache in the paediatric population. Safety results in paediatric patients were consistent with the safety profile of levetiracetam in adults except for behavioural and psychiatric adverse events which were more common in children than in adults (38.6% versus 18.6%). However, the relative risk was similar in children as compared to adults.

A study conducted in adults and adolescents with myoclonic seizures (12 to 65 years) showed that 33.3% of the patients in the Keppra group and 30.0% of the patients in the placebo group experienced undesirable effects that were judged to be related to treatment. The most commonly reported undesirable effects were headache and somnolence. The incidence of undesirable effects in patients with myoclonic seizures was lower than that in adult patients with partial onset seizures (33.3% versus 46.4%).

A study conducted in adults and children (4 to 65 years) with idiopathic generalised epilepsy with primary generalised tonic-clonic seizures showed that 39.2% of the patients in the Keppra group and 29.8% of the patients in the placebo group experienced undesirable effects that were judged to be related to treatment. The most commonly reported undesirable effect was fatigue.

Undesirable effects reported in clinical studies (adults and children) or from post-marketing experience are listed in the following table per System Organ Class and per frequency. For clinical trials, the frequency is defined as follows: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports. Data from post-marketing experience are insufficient to support an estimate of their incidence in the population to be treated.

- **General disorders and administration site conditions**
  Very common: asthenia/fatigue.

- **Nervous system disorders**
  Very common: somnolence
  Common: amnesia, ataxia, convulsion, dizziness, headache, hyperkinesia, tremor, balance disorder, disturbance in attention, memory impairment.
  Post-marketing experience: paraesthesia

- **Psychiatric disorders**
  Common: agitation, depression, emotional lability /mood swings, hostility/aggression, insomnia, nervousness/irritability, personality disorders, thinking abnormal
  Post-marketing experience: abnormal behaviour, anger, anxiety, confusion, hallucination, psychotic disorder, suicide, suicide attempt and suicidal ideation

- **Gastrointestinal disorders**
  Common: abdominal pain, diarrhoea, dyspepsia, nausea, vomiting
  Post-marketing experience: pancreatitis

- **Hepatobiliary disorders:**
Post-marketing experience: hepatic failure, hepatitis, liver function test abnormal

- Metabolism and nutrition disorders
Common: anorexia, weight increase.
The risk of anorexia is higher when topiramate is coadministered with levetiracetam.
Post-marketing experience: weight loss

- Ear and labyrinth disorders
Common: vertigo

- Eye disorders
Common: diplopia, vision blurred

- Musculoskeletal and connective tissue disorders
Common: myalgia

- Injury, poisoning and procedural complications
Common: accidental injury

- Infections and infestations
Common: infection, nasopharyngitis

- Respiratory, thoracic and mediastinal disorders
Common: cough increased

- Skin and subcutaneous tissue disorders
Common: rash, eczema, pruritus
Post-marketing experience: alopecia: in several cases, recovery was observed when Keppra was discontinued.

- Blood and lymphatic system disorders
Common: thrombocytopenia
Post-marketing experience: leukopenia, neutropenia, pancytopenia (with bone marrow suppression identified in some of the cases)

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: antiepileptics, ATC code: N03AX14.
The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances.

**Mechanism of action**

The mechanism of action of levetiracetam still remains to be fully elucidated but appears to be different from the mechanisms of current antiepileptic medicinal products. *In vitro* and *in vivo* experiments suggest that levetiracetam does not alter basic cell characteristics and normal neurotransmission. *In vitro* studies show that levetiracetam affects intraneuronal Ca2+ levels by partial inhibition of N-type Ca2+ currents and by reducing the release of Ca2+ 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.

**Clinical experience**

*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 adults, levetiracetam efficacy has been demonstrated in 3 double-blind, placebo-controlled studies at 1000 mg, 2000 mg, or 3000 mg/day, given in 2 divided doses, with a treatment duration of up to 18 weeks. In a pooled analysis, the percentage of patients who achieved 50% or greater reduction from baseline in the partial onset seizure frequency per week at stable dose (12/14 weeks) was of 27.7%, 31.6% and 41.3% for patients on 1000, 2000 or 3000 mg levetiracetam respectively and of 12.6% for patients on placebo.

In pediatric patients (4 to 16 years of age), levetiracetam efficacy was established in a double-blind, placebo-controlled study, which included 198 patients and had a treatment duration of 14 weeks. In this study, the patients received levetiracetam as a fixed dose of 60 mg/kg/day (with twice a day dosing). 44.6% of the levetiracetam treated patients and 19.6% of the patients on placebo had a 50% or greater reduction from baseline in the partial onset seizure frequency per week. With continued long-term treatment, 11.4% of the patients were seizure-free for at least 6 months and 7.2% were seizure-free for at least 1 year.

*Monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy.*

Efficacy of levetiracetam as monotherapy was established in a double-blind, parallel group, non-inferiority comparison to carbamazepine controlled release (CR) in 576 patients 16 years of age or older with newly or recently diagnosed epilepsy. The patients had to present with unprovoked partial
seizures or with generalized tonic-clonic seizures only. The patients were randomized to carbamazepine CR 400 – 1200 mg/day or levetiracetam 1000 – 3000 mg/day, the duration of the treatment was up to 121 weeks depending on the response. Six-month seizure freedom was achieved in 73.0% of levetiracetam-treated patients and 72.8% of carbamazepine-CR treated patients; the adjusted absolute difference between treatments was 0.2% (95% CI: -7.8 8.2). More than half of the subjects remained seizure free for 12 months (56.6% and 58.5% of subjects on levetiracetam and on carbamazepine CR respectively).

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

*Adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.*

Levetiracetam efficacy was established in a double-blind, placebo-controlled study of 16 weeks duration, in patients 12 years of age and older suffering from idiopathic generalized epilepsy with myoclonic seizures in different syndromes. The majority of patients presented with juvenile myoclonic epilepsy. In this study, levetiracetam dose was 3000 mg/day given in 2 divided doses. 58.3% of the levetiracetam treated patients and 23.3% of the patients on placebo had at least a 50% reduction in myoclonic seizure days per week. With continued long-term treatment, 28.6% of the patients were free of myoclonic seizures for at least 6 months and 21.0% were free of myoclonic seizures for at least 1 year.

*Adjunctive therapy in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalised epilepsy.*

Levetiracetam efficacy was established in a 24-week double-blind, placebo-controlled study, which included adults, adolescents and a limited number of children suffering from idiopathic generalized epilepsy with primary generalized tonic-clonic (PGTC) seizures in different syndromes (juvenile myoclonic epilepsy, juvenile absence epilepsy, childhood absence epilepsy, or epilepsy with Grand Mal seizures on awakening). In this study, levetiracetam dose was 3000 mg/day for adults and adolescents or 60 mg/kg/day for children, given in 2 divided doses. 72.2% of the levetiracetam treated patients and 45.2% of the patients on placebo had a 50% or greater decrease in the frequency of PGTC seizures per week. With continued long-term treatment, 47.4% of the patients were free of tonic-clonic seizures for at least 6 months and 31.5% were free of tonic-clonic seizures for at least 1 year.

### 5.2 Pharmacokinetic properties

Levetiracetam is a highly soluble and permeable compound. The pharmacokinetic profile is linear with low intra- and inter-subject variability. There is no modification of the clearance after repeated administration. There is no evidence for any relevant gender, race or circadian variability. The pharmacokinetic profile is comparable in healthy volunteers and in patients with epilepsy.

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

A significant correlation between saliva and plasma concentrations has been shown in adults and children (ratio of saliva/plasma concentrations ranged from 1 to 1.7 for oral tablet formulation and after 4 hours post-dose for oral solution formulation).

**Adults and adolescents**
Absorption

Levetiracetam is rapidly absorbed after oral administration. Oral absolute bioavailability is close to 100%.
Peak plasma concentrations (C_{max}) are achieved at 1.3 hours after dosing. Steady-state is achieved after two days of a twice daily administration schedule.
Peak concentrations (C_{max}) are typically 31 and 43 µg/ml following a single 1,000 mg dose and repeated 1,000 mg twice daily dose, respectively.
The extent of absorption is dose-independent and is not altered by food.

Distribution

No tissue distribution data are available in humans.
Neither levetiracetam nor its primary metabolite are significantly bound to plasma proteins (< 10 %).
The volume of distribution of levetiracetam is approximately 0.5 to 0.7 l/kg, a value close to the total body water volume.

Biotransformation

Levetiracetam is not extensively metabolised in humans. The major metabolic pathway (24 % of the dose) is an enzymatic hydrolysis of the acetamide group. Production of the primary metabolite, ucb L057, is not supported by liver cytochrome 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 Keppra with other substances, or vice versa, is unlikely.

Elimination

The plasma half-life in adults was 7±1 hours and did not vary either with dose, route of administration or repeated administration. The mean total body clearance was 0.96 ml/min/kg.

The major route of excretion was via urine, accounting for a mean 95 % of the dose (approximately 93 % of the dose was excreted within 48 hours). Excretion via faeces accounted for only 0.3 % of the dose.
The cumulative urinary excretion of levetiracetam and its primary metabolite accounted for 66 % and 24 % of the dose, respectively during the first 48 hours.
The renal clearance of levetiracetam and ucb L057 is 0.6 and 4.2 ml/min/kg respectively indicating that levetiracetam is excreted by glomerular filtration with subsequent tubular reabsorption and that
the primary metabolite is also excreted by active tubular secretion in addition to glomerular filtration. Levetiracetam elimination is correlated to creatinine clearance.

**Elderly**

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

**Children (4 to 12 years)**

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

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

**Infants and children (1 month to 4 years)**

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

**Renal impairment**

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

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

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

**Hepatic impairment**

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

**5.3 Preclinical safety data**

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.

In reproductive toxicity studies in the rat, levetiracetam induced developmental toxicity (increase in skeletal variations/minor anomalies, retarded growth, increased pup mortality) at exposure levels.
similar to or greater than the human exposure. In the rabbit foetal effects (embryonic death, increased skeletal anomalies, and increased malformations) were observed in the presence of maternal toxicity. The systemic exposure at the observed no effect level in the rabbit was about 4 to 5 times the human exposure.

Neonatal and juvenile animal studies in rats and dogs demonstrated that there were no adverse effects seen in any of the standard developmental or maturation endpoints at doses up to 1800 mg/kg/day corresponding to 30 times the maximum recommended human dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Sodium croscarmellose
Macrogol 6000
Colloidal anhydrous silica
Magnesium stearate

Film-coating Opadry 85F32004:
Polyvinyl alcohol-part. hydrolyzed
Titanium dioxide (E171)
Macrogol 3350
Talc
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Keppra 500 mg film-coated tablets are packaged in aluminium/PVC blisters placed into cardboard boxes containing 10, 20, 30, 50, 60, 100, 120 and 200 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

UCB Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
8. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/146/006
EU/1/00/146/007
EU/1/00/146/008
EU/1/00/146/009
EU/1/00/146/010
EU/1/00/146/011
EU/1/00/146/012
EU/1/00/146/013

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 September 2000
Date of last renewal: 08 July 2005

10. DATE OF REVISION OF THE TEXT
1. NAME OF THE MEDICINAL PRODUCT

Keppra 750 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 750 mg levetiracetam
Excipient: colouring agent E110.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
Orange, oblong, scored and debossed with the code “ucb” and “750” on one side.

4. CLINICAL PARTICULARS

4.1 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.

4.2 Posology and method of administration

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

• 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 (65 years and older)

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:

<table>
<thead>
<tr>
<th>Weight</th>
<th>Starting dose:</th>
<th>Maximum dose:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 mg/kg twice daily</td>
<td>30 mg/kg twice daily</td>
</tr>
<tr>
<td>15 kg</td>
<td>150 mg twice daily</td>
<td>450 mg twice daily</td>
</tr>
<tr>
<td>20 kg</td>
<td>200 mg twice daily</td>
<td>600 mg twice daily</td>
</tr>
<tr>
<td>25 kg</td>
<td>250 mg twice daily</td>
<td>750 mg twice daily</td>
</tr>
<tr>
<td>From 50 kg</td>
<td>500 mg twice daily</td>
<td>1500 mg twice daily</td>
</tr>
</tbody>
</table>

(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 (see section 5.2).

Patients with renal impairment

The daily dose must be individualised according to renal function.

For adult patients, refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in ml/min is needed. The CLcr in ml/min may be estimated from serum creatinine (mg/dl) determination using the following formula:

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

Then CLcr is adjusted for body surface area (BSA) as follows:

\[
\text{CLcr (ml/min/1.73 m²)} = \frac{\text{CLcr (ml/min)}}{\text{BSA subject (m²)}} \times 1.73
\]

Dosing adjustment for adult patients with impaired renal function

<table>
<thead>
<tr>
<th>Group</th>
<th>Creatinine clearance (ml/min/1.73m²)</th>
<th>Dosage and frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Function</td>
<td>Creatinine Clearance</td>
<td>Levetiracetam Dose</td>
</tr>
<tr>
<td>---------------</td>
<td>----------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Normal</td>
<td>&gt; 80</td>
<td>500 to 1,500 mg twice daily</td>
</tr>
<tr>
<td>Mild</td>
<td>50-79</td>
<td>500 to 1,000 mg twice daily</td>
</tr>
<tr>
<td>Moderate</td>
<td>30-49</td>
<td>250 to 750 mg twice daily</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt; 30</td>
<td>250 to 500 mg twice daily</td>
</tr>
<tr>
<td>End-stage renal disease patients</td>
<td>-</td>
<td>500 to 1,000 mg once daily (2)</td>
</tr>
</tbody>
</table>

(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.

4.3 Contraindications

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

4.4 Special warnings and special precautions for use

In accordance with current clinical practice, if Keppra has to be discontinued it is recommended to withdraw it gradually (e.g. in adults: 500 mg 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 section 4.2).

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.

Keppra 750 mg film-coated tablets contain E110 colouring agent (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Pre-marketing data from clinical studies conducted in adults indicate that Keppra did not influence the serum concentrations of existing antiepileptic medicinal products (phenytoin, carbamazepine, valproic
acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these antiepileptic medicinal
products did not influence the pharmacokinetics of Keppra.

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.

4.6 Pregnancy and lactation

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

Levetiracetam is excreted in human breast milk. Therefore, breast-feeding 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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.
Due to possible different individual sensitivity, some patients might experience somnolence or other
central nervous system related symptoms, 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.

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

In monotherapy 49.8% of the subjects experienced at least one drug related undesirable effect. The most frequently reported undesirable effects were fatigue and somnolence.

A study conducted in paediatric patients (4 to 16 years) with partial onset seizures showed that 55.4% of the patients in the Keppra group and 40.2% of the patients in the placebo group experienced undesirable effects. Serious undesirable effects were experienced in 0.0% of the patients in the Keppra group and 1.0% of the patients in the placebo group. The most commonly reported undesirable effects were somnolence, hostility, nervousness, emotional lability, agitation, anorexia, asthenia and headache in the paediatric population. Safety results in paediatric patients were consistent with the safety profile of levetiracetam in adults except for behavioural and psychiatric adverse events which were more common in children than in adults (38.6% versus 18.6%). However, the relative risk was similar in children as compared to adults.

A study conducted in adults and adolescents with myoclonic seizures (12 to 65 years) showed that 33.3% of the patients in the Keppra group and 30.0% of the patients in the placebo group experienced undesirable effects that were judged to be related to treatment. The most commonly reported undesirable effects were headache and somnolence. The incidence of undesirable effects in patients with myoclonic seizures was lower than that in adult patients with partial onset seizures (33.3% versus 46.4%).

A study conducted in adults and children (4 to 65 years) with idiopathic generalised epilepsy with primary generalised tonic-clonic seizures showed that 39.2% of the patients in the Keppra group and 29.8% of the patients in the placebo group experienced undesirable effects that were judged to be related to treatment. The most commonly reported undesirable effect was fatigue.

Undesirable effects reported in clinical studies (adults and children) or from post-marketing experience are listed in the following table per System Organ Class and per frequency. For clinical trials, the frequency is defined as follows: very common (≥1/10); common (≥ 1/100, <1/10); uncommon (≥ 1/1,000, <1/100); rare (≥ 1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports. Data from post-marketing experience are insufficient to support an estimate of their incidence in the population to be treated.

- **General disorders and administration site conditions**
  Very common: asthenia/fatigue.

- **Nervous system disorders**
  Very common: somnolence
  Common: amnesia, ataxia, convulsion, dizziness, headache, hyperkinesia, tremor, balance disorder, disturbance in attention, memory impairment.
  Post-marketing experience: paraesthesia

- **Psychiatric disorders**
  Common: agitation, depression, emotional lability/mood swings, hostility/aggression, insomnia, nervousness/irritability, personality disorders, thinking abnormal
  Post-marketing experience: abnormal behaviour, anger, anxiety, confusion, hallucination, psychotic disorder, suicide, suicide attempt and suicidal ideation
- Gastrointestinal disorders
  Common: abdominal pain, diarrhoea, dyspepsia, nausea, vomiting
  Post-marketing experience: pancreatitis

- Hepatobiliary disorders:
  Post-marketing experience: hepatic failure, hepatitis, liver function test abnormal

- Metabolism and nutrition disorders
  Common: anorexia, weight increase.
  The risk of anorexia is higher when topiramate is coadministered with levetiracetam.
  Post-marketing experience: weight loss

- Ear and labyrinth disorders
  Common: vertigo

- Eye disorders
  Common: diplopia, vision blurred

- Musculoskeletal and connective tissue disorders
  Common: myalgia

- Injury, poisoning and procedural complications
  Common: accidental injury

- Infections and infestations
  Common: infection, nasopharyngitis

- Respiratory, thoracic and mediastinal disorders
  Common: cough increased

- Skin and subcutaneous tissue disorders
  Common: rash, eczema, pruritus
  Post-marketing experience: alopecia: in several cases, recovery was observed when Keppra was discontinued.

- Blood and lymphatic system disorders
  Common: thrombocytopenia
  Post-marketing experience: leukopenia, neutropenia, pancytopenia (with bone marrow suppression identified in some of the cases)

E 110 coloring agent may cause allergic reactions.

4.9 Overdose

Symptoms

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

Management of overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiepileptics, ATC code: N03AX14.
The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances.

Mechanism of action

The mechanism of action of levetiracetam still remains to be fully elucidated but appears to be different from the mechanisms of current antiepileptic medicinal products. In vitro and in vivo experiments suggest that levetiracetam does not alter basic cell characteristics and normal neurotransmission. In vitro studies show that levetiracetam affects intraneuronal Ca2+ levels by partial inhibition of N-type Ca2+ currents and by reducing the release of Ca2+ 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.

Clinical experience

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 adults, levetiracetam efficacy has been demonstrated in 3 double-blind, placebo-controlled studies at 1000 mg, 2000 mg, or 3000 mg/day, given in 2 divided doses, with a treatment duration of up to 18 weeks. In a pooled analysis, the percentage of patients who achieved 50% or greater reduction from baseline in the partial onset seizure frequency per week at stable dose (12/14 weeks) was of 27.7%, 31.6% and 41.3% for patients on 1000, 2000 or 3000 mg levetiracetam respectively and of 12.6% for patients on placebo.

In pediatric patients (4 to 16 years of age), levetiracetam efficacy was established in a double-blind, placebo-controlled study, which included 198 patients and had a treatment duration of 14 weeks. In this study, the patients received levetiracetam as a fixed dose of 60 mg/kg/day (with twice a day dosing). 44.6% of the levetiracetam treated patients and 19.6% of the patients on placebo had a 50% or greater reduction from baseline in the partial onset seizure frequency per week. With continued long-term
treatment, 11.4% of the patients were seizure-free for at least 6 months and 7.2% were seizure-free for at least 1 year.

Monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy.

Efficacy of levetiracetam as monotherapy was established in a double-blind, parallel group, non-inferiority comparison to carbamazepine controlled release (CR) in 576 patients 16 years of age or older with newly or recently diagnosed epilepsy. The patients had to present with unprovoked partial seizures or with generalized tonic-clonic seizures only. The patients were randomized to carbamazepine CR 400 – 1200 mg/day or levetiracetam 1000 – 3000 mg/day, the duration of the treatment was up to 121 weeks depending on the response. Six-month seizure freedom was achieved in 73.0% of levetiracetam-treated patients and 72.8% of carbamazepine-CR treated patients; the adjusted absolute difference between treatments was 0.2% (95% CI: -7.8 8.2). More than half of the subjects remained seizure free for 12 months (56.6% and 58.5% of subjects on levetiracetam and on carbamazepine CR respectively).

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

Adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.

Levetiracetam efficacy was established in a double-blind, placebo-controlled study of 16 weeks duration, in patients 12 years of age and older suffering from idiopathic generalized epilepsy with myoclonic seizures in different syndromes. The majority of patients presented with juvenile myoclonic epilepsy. In this study, levetiracetam, dose was 3000 mg/day given in 2 divided doses. 58.3% of the levetiracetam treated patients and 23.3% of the patients on placebo had at least a 50% reduction in myoclonic seizure days per week. With continued long-term treatment, 28.6% of the patients were free of myoclonic seizures for at least 6 months and 21.0% were free of myoclonic seizures for at least 1 year.

Adjunctive therapy in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalised epilepsy.

Levetiracetam efficacy was established in a 24-week double-blind, placebo-controlled study, which included adults, adolescents and a limited number of children suffering from idiopathic generalized epilepsy with primary generalized tonic-clonic (PGTC) seizures in different syndromes (juvenile myoclonic epilepsy, juvenile absence epilepsy, childhood absence epilepsy, or epilepsy with Grand Mal seizures on awakening). In this study, levetiracetam dose was 3000 mg/day for adults and adolescents or 60 mg/kg/day for children, given in 2 divided doses. 72.2% of the levetiracetam treated patients and 45.2% of the patients on placebo had a 50% or greater decrease in the frequency of PGTC seizures per week. With continued long-term treatment, 47.4% of the patients were free of tonic-clonic seizures for at least 6 months and 31.5% were free of tonic-clonic seizures for at least 1 year.

5.2 Pharmacokinetic properties

Levetiracetam is a highly soluble and permeable compound. The pharmacokinetic profile is linear with low intra- and inter-subject variability. There is no modification of the clearance after repeated administration. There is no evidence for any relevant gender, race or circadian variability. The pharmacokinetic profile is comparable in healthy volunteers and in patients with epilepsy.
Due to its complete and linear absorption, plasma levels can be predicted from the oral dose of levetiracetam expressed as mg/kg bodyweight. Therefore there is no need for plasma level monitoring of levetiracetam.

A significant correlation between saliva and plasma concentrations has been shown in adults and children (ratio of saliva/plasma concentrations ranged from 1 to 1.7 for oral tablet formulation and after 4 hours post-dose for oral solution formulation).

**Adults and adolescents**

**Absorption**

Levetiracetam is rapidly absorbed after oral administration. Oral absolute bioavailability is close to 100%. Peak plasma concentrations (C_{max}) are achieved at 1.3 hours after dosing. Steady-state is achieved after two days of a twice daily administration schedule. Peak concentrations (C_{max}) are typically 31 and 43 µg/ml following a single 1,000 mg dose and repeated 1,000 mg twice daily dose, respectively. The extent of absorption is dose-independent and is not altered by food.

**Distribution**

No tissue distribution data are available in humans. Neither levetiracetam nor its primary metabolite are significantly bound to plasma proteins (<10 %). The volume of distribution of levetiracetam is approximately 0.5 to 0.7 l/kg, a value close to the total body water volume.

**Biotransformation**

Levetiracetam is not extensively metabolised in humans. The major metabolic pathway (24 % of the dose) is an enzymatic hydrolysis of the acetamide group. Production of the primary metabolite, ucb L057, is not supported by liver cytochrome 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 Keppra with other substances, or vice versa, is unlikely.

**Elimination**

The plasma half-life in adults was 7±1 hours and did not vary either with dose, route of administration or repeated administration. The mean total body clearance was 0.96 ml/min/kg.
The major route of excretion was via urine, accounting for a mean 95 % of the dose (approximately 93 % of the dose was excreted within 48 hours). Excretion via faeces accounted for only 0.3 % of the dose. 

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

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

Elderly

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

Children (4 to 12 years)

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

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

Infants and children (1 month to 4 years)

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

Renal impairment

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

In anuric end-stage renal disease adult subjects the half-life was approximately 25 and 3.1 hours during interdialytic and intradialytic periods, respectively. The fractional removal of levetiracetam was 51 % during a typical 4-hour dialysis session.

Hepatic impairment

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

5.3 Preclinical safety data
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.

In reproductive toxicity studies in the rat, levetiracetam induced developmental toxicity (increase in skeletal variations/minor anomalies, retarded growth, increased pup mortality) at exposure levels similar to or greater than the human exposure. In the rabbit foetal effects (embryonic death, increased skeletal anomalies, and increased malformations) were observed in the presence of maternal toxicity. The systemic exposure at the observed no effect level in the rabbit was about 4 to 5 times the human exposure.

Neonatal and juvenile animal studies in rats and dogs demonstrated that there were no adverse effects seen in any of the standard developmental or maturation endpoints at doses up to 1800 mg/kg/day corresponding to 30 times the maximum recommended human dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Sodium croscarmellose
Macrogol 6000
Colloidal anhydrous silica.
Magnesium stearate

Film-coating Opadry 85F23452:
Polyvinyl alcohol-part. hydrolyzed
Titanium dioxide (E171)
Macrogol 3350
Talc
Sunset yellow FCF aluminium lake (E110)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Keppra 750 mg film-coated tablets are packaged in aluminium/PVC blisters placed into cardboard boxes containing 20, 30, 50, 60, 80, 100 and 200 film-coated tablets. Not all pack sizes may be marketed.
6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/146/014
EU/1/00/146/015
EU/1/00/146/016
EU/1/00/146/017
EU/1/00/146/018
EU/1/00/146/019
EU/1/00/146/028

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 September 2000
Date of last renewal: 08 July 2005

10. DATE OF REVISION OF THE TEXT
1. NAME OF THE MEDICINAL PRODUCT

Keppra 1000 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 1,000 mg levetiracetam.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
White, oblong, scored and debossed with the code “ucb” and “1000” on one side.

4. CLINICAL PARTICULARS

4.1 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.

4.2 Posology and method of administration

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

• 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 (65 years and older)
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:

<table>
<thead>
<tr>
<th>Weight</th>
<th>Starting dose:</th>
<th>Maximum dose:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 mg/kg twice daily</td>
<td>30 mg/kg twice daily</td>
</tr>
<tr>
<td>15 kg</td>
<td>150 mg twice daily</td>
<td>450 mg twice daily</td>
</tr>
<tr>
<td>20 kg</td>
<td>200 mg twice daily</td>
<td>600 mg twice daily</td>
</tr>
<tr>
<td>25 kg</td>
<td>250 mg twice daily</td>
<td>750 mg twice daily</td>
</tr>
<tr>
<td>From 50 kg</td>
<td>500 mg twice daily</td>
<td>1500 mg twice daily</td>
</tr>
</tbody>
</table>

(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 (see section 5.2).

**Patients with renal impairment**

The daily dose must be individualised according to renal function.

For adult patients, refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in ml/min is needed. The CLcr in ml/min may be estimated from serum creatinine (mg/dl) determination using the following formula:

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

Then CLcr is adjusted for body surface area (BSA) as follows:

\[
\text{CLcr (ml/min/1.73 m²)} = \frac{\text{CLcr (ml/min)}}{\text{BSA subject (m2)}} \times 1.73
\]

Dosing adjustment for adult patients with impaired renal function:

<table>
<thead>
<tr>
<th>Group</th>
<th>Creatinine clearance (ml/min/1.73m²)</th>
<th>Dosage and frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt; 80</td>
<td>500 to 1,500 mg twice daily</td>
</tr>
<tr>
<td>Mild</td>
<td>50-79</td>
<td>500 to 1,000 mg twice daily</td>
</tr>
<tr>
<td>Renal Function</td>
<td>Levetiracetam Dose</td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------------------</td>
<td></td>
</tr>
<tr>
<td>Moderate (30-49)</td>
<td>250 to 750 mg twice daily</td>
<td></td>
</tr>
<tr>
<td>Severe (&lt; 30)</td>
<td>250 to 500 mg twice daily</td>
<td></td>
</tr>
<tr>
<td>End-stage renal disease patients Undergoing dialysis (1)</td>
<td>500 to 1,000 mg once daily (2)</td>
<td></td>
</tr>
</tbody>
</table>

(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.

4.3 Contraindications

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

4.4 Special warnings and special precautions for use

In accordance with current clinical practice, if Keppra has to be discontinued it is recommended to withdraw it gradually (e.g. in adults: 500 mg 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 section 4.2).

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.

4.5 Interaction with other medicinal products and other forms of interaction

Pre-marketing data from clinical studies conducted in adults indicate that Keppra did not influence the serum concentrations of existing antiepileptic medicinal products (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these antiepileptic medicinal products did not influence the pharmacokinetics of Keppra.

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.

4.6 Pregnancy and lactation

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

Levetiracetam is excreted in human breast milk. Therefore, breast-feeding 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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Due to possible different individual sensitivity, some patients might experience somnolence or other central nervous system related symptoms, 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.

4.8 Undesirable effects

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

In monotherapy 49.8 % of the subjects experienced at least one drug related undesirable effect. The most frequently reported undesirable effects were fatigue and somnolence.

A study conducted in paediatric patients (4 to 16 years) with partial onset seizures showed that 55.4 % of the patients in the Keppra group and 40.2 % of the patients in the placebo group experienced undesirable effects. Serious undesirable effects were experienced in 0.0 % of the patients in the Keppra group and 1.0 % of the patients in the placebo group. The most commonly reported undesirable effects were somnolence, hostility, nervousness, emotional lability, agitation, anorexia, asthenia and headache in the paediatric population. Safety results in paediatric patients were consistent with the safety profile of levetiracetam in adults except for behavioural and psychiatric adverse events which were more common in children than in adults (38.6% versus 18.6%). However, the relative risk was similar in children as compared to adults.

A study conducted in adults and adolescents with myoclonic seizures (12 to 65 years) showed that 33.3% of the patients in the Keppra group and 30.0% of the patients in the placebo group experienced undesirable effects that were judged to be related to treatment. The most commonly reported undesirable effects were headache and somnolence. The incidence of undesirable effects in patients with myoclonic seizures was lower than that in adult patients with partial onset seizures (33.3% versus 46.4%).

A study conducted in adults and children (4 to 65 years) with idiopathic generalised epilepsy with primary generalised tonic-clonic seizures showed that 39.2 % of the patients in the Keppra group and 29.8 % of the patients in the placebo group experienced undesirable effects that were judged to be related to treatment. The most commonly reported undesirable effect was fatigue.

Undesirable effects reported in clinical studies (adults and children) or from post-marketing experience are listed in the following table per System Organ Class and per frequency. For clinical trials, the frequency is defined as follows: very common (≥1/10); common (≥ 1/100, <1/10); uncommon (≥ 1/1,000, <1/100); rare (≥ 1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports. Data from post-marketing experience are insufficient to support an estimate of their incidence in the population to be treated.

- **General disorders and administration site conditions**
  Very common: asthenia/fatigue.

- **Nervous system disorders**
  Very common: somnolence
  Common: amnesia, ataxia, convulsion, dizziness, headache, hyperkinesia, tremor, balance disorder, disturbance in attention, memory impairment.
  Post-marketing experience: paraesthesia

- **Psychiatric disorders**
  Common: agitation, depression, emotional lability/mood swings, hostility/aggression, insomnia, nervousness/irritability, personality disorders, thinking abnormal
  Post-marketing experience: abnormal behaviour, anger, anxiety, confusion, hallucination, psychotic disorder, suicide, suicide attempt and suicidal ideation

- **Gastrointestinal disorders**
  Common: abdominal pain, diarrhoea, dyspepsia, nausea, vomiting
  Post-marketing experience: pancreatitis
- **Hepatobiliary disorders:**
  Post-marketing experience: hepatic failure, hepatitis, liver function test abnormal

- **Metabolism and nutrition disorders**
  Common: anorexia, weight increase.  
The risk of anorexia is higher when topiramate is coadministered with levetiracetam.  
Post-marketing experience: weight loss

- **Ear and labyrinth disorders**
  Common: vertigo

- **Eye disorders**
  Common: diplopia, vision blurred

- **Musculoskeletal and connective tissue disorders**
  Common: myalgia

- **Injury, poisoning and procedural complications**
  Common: accidental injury

- **Infections and infestations**
  Common: infection, nasopharyngitis

- **Respiratory, thoracic and mediastinal disorders**
  Common: cough increased

- **Skin and subcutaneous tissue disorders**
  Common: rash, eczema, pruritus  
Post-marketing experience: alopecia: in several cases, recovery was observed when Keppra was discontinued.

- **Blood and lymphatic system disorders**
  Common: thrombocytopenia  
Post-marketing experience: leukopenia, neutropenia, pancytopenia (with bone marrow suppression identified in some of the cases)

### 4.9 Overdose

**Symptoms**

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

**Management of overdose**

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

### 5. PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties
Pharmacotherapeutic group: antiepileptics, ATC code: N03AX14.
The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances.

Mechanism of action

The mechanism of action of levetiracetam still remains to be fully elucidated but appears to be different from the mechanisms of current antiepileptic medicinal products. In vitro and in vivo experiments suggest that levetiracetam does not alter basic cell characteristics and normal neurotransmission. In vitro studies show that levetiracetam affects intraneuronal Ca2+ levels by partial inhibition of N-type Ca2+ currents and by reducing the release of Ca2+ 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.

Clinical experience

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 adults, levetiracetam efficacy has been demonstrated in 3 double-blind, placebo-controlled studies at 1000 mg, 2000 mg, or 3000 mg/day, given in 2 divided doses, with a treatment duration of up to 18 weeks. In a pooled analysis, the percentage of patients who achieved 50% or greater reduction from baseline in the partial onset seizure frequency per week at stable dose (12/14 weeks) was of 27.7%, 31.6% and 41.3% for patients on 1000, 2000 or 3000 mg levetiracetam respectively and of 12.6% for patients on placebo.

In pediatric patients (4 to 16 years of age), levetiracetam efficacy was established in a double-blind, placebo-controlled study, which included 198 patients and had a treatment duration of 14 weeks. In this study, the patients received levetiracetam as a fixed dose of 60 mg/kg/day (with twice a day dosing). 44.6% of the levetiracetam treated patients and 19.6% of the patients on placebo had a 50% or greater reduction from baseline in the partial onset seizure frequency per week. With continued long-term treatment, 11.4% of the patients were seizure-free for at least 6 months and 7.2% were seizure-free for at least 1 year.

Monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy.

Efficacy of levetiracetam as monotherapy was established in a double-blind, parallel group, non-inferiority comparison to carbamazepine controlled release (CR) in 576 patients 16 years of age or
older with newly or recently diagnosed epilepsy. The patients had to present with unprovoked partial seizures or with generalized tonic-clonic seizures only. The patients were randomized to carbamazepine CR 400 – 1200 mg/day or levetiracetam 1000 – 3000 mg/day, the duration of the treatment was up to 121 weeks depending on the response. Six-month seizure freedom was achieved in 73.0% of levetiracetam-treated patients and 72.8% of carbamazepine-CR treated patients; the adjusted absolute difference between treatments was 0.2% (95% CI: -7.8 8.2). More than half of the subjects remained seizure free for 12 months (56.6% and 58.5% of subjects on levetiracetam and on carbamazepine CR respectively).

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

**Adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.**

Levetiracetam efficacy was established in a double-blind, placebo-controlled study of 16 weeks duration, in patients 12 years of age and older suffering from idiopathic generalized epilepsy with myoclonic seizures in different syndromes. The majority of patients presented with juvenile myoclonic epilepsy. In this study, levetiracetam, dose was 3000 mg/day given in 2 divided doses. 58.3% of the levetiracetam treated patients and 23.3% of the patients on placebo had at least a 50% reduction in myoclonic seizure days per week. With continued long-term treatment, 28.6% of the patients were free of myoclonic seizures for at least 6 months and 21.0% were free of myoclonic seizures for at least 1 year.

**Adjunctive therapy in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalised epilepsy.**

Levetiracetam efficacy was established in a 24-week double-blind, placebo-controlled study which included adults, adolescents and a limited number of children suffering from idiopathic generalized epilepsy with primary generalized tonic-clonic (PGTC) seizures in different syndromes (juvenile myoclonic epilepsy, juvenile absence epilepsy, childhood absence epilepsy, or epilepsy with Grand Mal seizures on awakening). In this study, levetiracetam dose was 3000 mg/day for adults and adolescents or 60 mg/kg/day for children, given in 2 divided doses. 72.2% of the levetiracetam treated patients and 45.2% of the patients on placebo had a 50% or greater decrease in the frequency of PGTC seizures per week. With continued long-term treatment, 47.4% of the patients were free of tonic-clonic seizures for at least 6 months and 31.5% were free of tonic-clonic seizures for at least 1 year.

### 5.2 Pharmacokinetic properties

Levetiracetam is a highly soluble and permeable compound. The pharmacokinetic profile is linear with low intra- and inter-subject variability. There is no modification of the clearance after repeated administration. There is no evidence for any relevant gender, race or circadian variability. The pharmacokinetic profile is comparable in healthy volunteers and in patients with epilepsy.

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

A significant correlation between saliva and plasma concentrations has been shown in adults and children (ratio of saliva/plasma concentrations ranged from 1 to 1.7 for oral tablet formulation and after 4 hours post-dose for oral solution formulation).

**Adults and adolescents**
Absorption

Levetiracetam is rapidly absorbed after oral administration. Oral absolute bioavailability is close to 100%.
Peak plasma concentrations ($C_{\text{max}}$) are achieved at 1.3 hours after dosing. Steady-state is achieved after two days of a twice daily administration schedule.
Peak concentrations ($C_{\text{max}}$) are typically 31 and 43 µg/ml following a single 1,000 mg dose and repeated 1,000 mg twice daily dose, respectively.
The extent of absorption is dose-independent and is not altered by food.

Distribution

No tissue distribution data are available in humans.
Neither levetiracetam nor its primary metabolite are significantly bound to plasma proteins (< 10 %).
The volume of distribution of levetiracetam is approximately 0.5 to 0.7 l/kg, a value close to the total body water volume.

Biotransformation

Levetiracetam is not extensively metabolised in humans. The major metabolic pathway (24 % of the dose) is an enzymatic hydrolysis of the acetamide group. Production of the primary metabolite, ucb L057, is not supported by liver cytochrome P450 isoforms. Hydrolysis of the acetamide group was measurable in a large number of tissues including blood cells. The metabolite ucb L057 is pharmacologically inactive.

Two minor metabolites were also identified. One was obtained by hydroxylation of the pyrrolidone ring (1.6 % of the dose) and the other one by opening of the pyrrolidone ring (0.9 % of the dose). Other unidentified components accounted 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 Keppra with other substances, or vice versa, is unlikely.

Elimination

The plasma half-life in adults was 7±1 hours and did not vary either with dose, route of administration or repeated administration. The mean total body clearance was 0.96 ml/min/kg.
The major route of excretion was via urine, accounting for a mean 95 % of the dose (approximately 93 % of the dose was excreted within 48 hours). Excretion via faeces accounted for only 0.3 % of the dose.
The cumulative urinary excretion of levetiracetam and its primary metabolite accounted for 66 % and 24 % of the dose, respectively during the first 48 hours.
The renal clearance of levetiracetam and ucb L057 is 0.6 and 4.2 ml/min/kg respectively indicating that levetiracetam is excreted by glomerular filtration with subsequent tubular reabsorption and that
the primary metabolite is also excreted by active tubular secretion in addition to glomerular filtration. Levetiracetam elimination is correlated to creatinine clearance.

**Elderly**

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

**Children (4 to 12 years)**

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

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

**Infants and children (1 month to 4 years)**

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

**Renal impairment**

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

In anuric end-stage renal disease adult subjects the half-life was approximately 25 and 3.1 hours during interdialytic and intradialytic periods, respectively. The fractional removal of levetiracetam was 51% during a typical 4-hour dialysis session.

**Hepatic impairment**

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

5.3 **Preclinical safety data**

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.

In reproductive toxicity studies in the rat, levetiracetam induced developmental toxicity (increase in skeletal variations/minor anomalies, retarded growth, increased pup mortality) at exposure levels
similar to or greater than the human exposure. In the rabbit foetal effects (embryonic death, increased skeletal anomalies, and increased malformations) were observed in the presence of maternal toxicity. The systemic exposure at the observed no effect level in the rabbit was about 4 to 5 times the human exposure.

Neonatal and juvenile animal studies in rats and dogs demonstrated that there were no adverse effects seen in any of the standard developmental or maturation endpoints at doses up to 1800 mg/kg/day corresponding to 30 times the maximum recommended human dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Sodium croscarmellose
Macrogol 6000
Colloidal anhydrous silica
Magnesium stearate

Film-coating Opadry 85F18422:
Polyvinyl alcohol-part. hydrolyzed
Titanium dioxide (E171)
Macrogol 3350
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Keppra 1000 mg film-coated tablets are packaged in aluminium/PVC blisters placed into cardboard boxes containing 10, 20, 30, 50, 60, 100 and 200 film-coated tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

UCB Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium
8. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/146/020
EU/1/00/146/021
EU/1/00/146/022
EU/1/00/146/023
EU/1/00/146/024
EU/1/00/146/025
EU/1/00/146/026

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 September 2000
Date of last renewal: 08 July 2005

10. DATE OF REVISION OF THE TEXT
1. **NAME OF THE MEDICINAL PRODUCT**

Keppra 100 mg/ml oral solution.

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each ml contains 100 mg levetiracetam
Excipients: methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216) and 300 mg maltitol.

For a full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Oral solution.
Clear liquid.

4. **CLINICAL PARTICULARS**

4.1 **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.

4.2 **Posology and method of administration**

The oral solution may be diluted in a glass of water and may be taken with or without food. A graduated oral syringe and instructions for use in the package leaflet are provided with Keppra.

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 (65 years and older)**

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:**

<table>
<thead>
<tr>
<th>Weight</th>
<th>Starting dose: 10 mg/kg twice daily</th>
<th>Maximum dose: 30 mg/kg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 kg</td>
<td>150 mg twice daily</td>
<td>450 mg twice daily</td>
</tr>
<tr>
<td>20 kg</td>
<td>200 mg twice daily</td>
<td>600 mg twice daily</td>
</tr>
<tr>
<td>25 kg</td>
<td>250 mg twice daily</td>
<td>750 mg twice daily</td>
</tr>
<tr>
<td>From 50 kg</td>
<td>500 mg twice daily</td>
<td>1500 mg twice daily</td>
</tr>
</tbody>
</table>

(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.

The graduated oral syringe contains up to 1,000 mg levetiracetam (corresponding to 10 ml) with a graduation every 25 mg (corresponding to 0.25 ml).

**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 (see section 5.2).

**Patients with renal impairment**

The daily dose must be individualised according to renal function.

For adult patients, refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in ml/min is needed. The CLcr in ml/min may be estimated from serum creatinine (mg/dl) determination using the following formula:

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

Then CLcr is adjusted for body surface area (BSA) as follows:

$$\text{CLcr (ml/min/1.73 m}^2) = \frac{\text{CLcr (ml/min)}}{\text{BSA subject (m2)}} \times 1.73$$
Dosing adjustment for adult patients with impaired renal function

<table>
<thead>
<tr>
<th>Group</th>
<th>Creatinine clearance (ml/min/1.73m²)</th>
<th>Dosage and frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt; 80</td>
<td>500 to 1,500 mg twice daily</td>
</tr>
<tr>
<td>Mild</td>
<td>50-79</td>
<td>500 to 1,000 mg twice daily</td>
</tr>
<tr>
<td>Moderate</td>
<td>30-49</td>
<td>250 to 750 mg twice daily</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt; 30</td>
<td>250 to 500 mg twice daily</td>
</tr>
<tr>
<td>End-stage renal disease patients</td>
<td>-</td>
<td>500 to 1,000 mg once daily (2)</td>
</tr>
<tr>
<td>Undergoing dialysis (1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(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.

4.3 Contraindications

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

4.4 Special warnings and special precautions for use

In accordance with current clinical practice, if Keppra has to be discontinued it is recommended to withdraw it gradually (e.g. in adults: 500 mg 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 section 4.2).

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.

Keppra 100 mg/ml oral solution includes methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) which may cause allergic reactions (possibly delayed).
It also includes maltitol; patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Pre-marketing data from clinical studies conducted in adults indicate that Keppra did not influence the serum concentrations of existing antiepileptic medicinal products (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these antiepileptic medicinal products did not influence the pharmacokinetics of Keppra.

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 (ethinylestradiol and levonorgestrel); endocrine parameters (luteinizing hormone and progesterone) were not modified. Levetiracetam 2,000 mg daily did not influence the pharmacokinetics of digoxin and warfarin; prothrombin times were not modified. Co-administration with digoxin, oral contraceptives and warfarin did not influence the pharmacokinetics of levetiracetam.

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

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

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

4.6 Pregnancy and lactation

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

Levetiracetam is excreted in human breast milk. Therefore, breast-feeding 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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.
Due to possible different individual sensitivity, some patients might experience somnolence or other central nervous system related symptoms, 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.

4.8 Undesirable effects

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

In monotherapy 49.8% of the subjects experienced at least one drug related undesirable effect. The most frequently reported undesirable effects were fatigue and somnolence.

A study conducted in paediatric patients (4 to 16 years) with partial onset seizures showed that 55.4% of the patients in the Keppra group and 40.2% of the patients in the placebo group experienced undesirable effects. Serious undesirable effects were experienced in 0.0% of the patients in the Keppra group and 1.0% of the patients in the placebo group. The most commonly reported undesirable effects were somnolence, hostility, nervousness, emotional lability, agitation, anorexia, asthenia and headache in the paediatric population. Safety results in paediatric patients were consistent with the safety profile of levetiracetam in adults except for behavioural and psychiatric adverse events which were more common in children than in adults (38.6% versus 18.6%). However, the relative risk was similar in children as compared to adults.

A study conducted in adults and adolescents with myoclonic seizures (12 to 65 years) showed that 33.3% of the patients in the Keppra group and 30.0% of the patients in the placebo group experienced undesirable effects that were judged to be related to treatment. The most commonly reported undesirable effects were headache and somnolence. The incidence of undesirable effects in patients with myoclonic seizures was lower than that in adult patients with partial onset seizures (33.3% versus 46.4%).

A study conducted in adults and children (4 to 65 years) with idiopathic generalised epilepsy with primary generalised tonic-clonic seizures showed that 39.2% of the patients in the Keppra group and 29.8% of the patients in the placebo group experienced undesirable effects that were judged to be related to treatment. The most commonly reported undesirable effect was fatigue.

Undesirable effects reported in clinical studies (adults and children) or from post-marketing experience are listed in the following table per System Organ Class and per frequency. For clinical trials, the frequency is defined as follows: very common (≥1/10); common (≥ 1/100, <1/10); uncommon (≥ 1/1,000, <1/100); rare (≥ 1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports. Data from post-marketing experience are insufficient to support an estimate of their incidence in the population to be treated.

- General disorders and administration site conditions
  Very common: asthenia/fatigue.

- Nervous system disorders
  Very common: somnolence
  Common: amnesia, ataxia, convulsion, dizziness, headache, hyperkinesia, tremor, balance disorder, disturbance in attention, memory impairment.
Post-marketing experience: paraesthesia

- Psychiatric disorders
  Common: agitation, depression, emotional lability/mood swings, hostility/aggression, insomnia, nervousness/irritability, personality disorders, thinking abnormal
  Post-marketing experience: abnormal behaviour, anger, anxiety, confusion, hallucination, psychotic disorder, suicide, suicide attempt and suicidal ideation

- Gastrointestinal disorders
  Common: abdominal pain, diarrhoea, dyspepsia, nausea, vomiting
  Post-marketing experience: pancreatitis

- Hepatobiliary disorders:
  Post-marketing experience: hepatic failure, hepatitis, liver function test abnormal

- Metabolism and nutrition disorders
  Common: anorexia, weight increase.
  The risk of anorexia is higher when topiramate is coadministered with levetiracetam.
  Post-marketing experience: weight loss

- Ear and labyrinth disorders
  Common: vertigo

- Eye disorders
  Common: diplopia, vision blurred

- Musculoskeletal and connective tissue disorders
  Common: myalgia

- Injury, poisoning and procedural complications
  Common: accidental injury

- Infections and infestations
  Common: infection, nasopharyngitis

- Respiratory, thoracic and mediastinal disorders
  Common: cough increased

- Skin and subcutaneous tissue disorders
  Common: rash, eczema, pruritus
  Post-marketing experience: alopecia: in several cases, recovery was observed when Keppra was discontinued.

- Blood and lymphatic system disorders
  Common: thrombocytopenia
  Post-marketing experience: leukopenia, neutropenia, pancytopenia (with bone marrow suppression identified in some of the cases).

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiepileptics, ATC code: N03AX14

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

Mechanism of action

The mechanism of action of levetiracetam still remains to be fully elucidated but appears to be different from the mechanisms of current antiepileptic medicinal products. In vitro and in vivo experiments suggest that levetiracetam does not alter basic cell characteristics and normal neurotransmission. In vitro studies show that levetiracetam affects intraneuronal Ca2+ levels by partial inhibition of N-type Ca2+ currents and by reducing the release of Ca2+ 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.

Clinical experience

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 adults, levetiracetam efficacy has been demonstrated in 3 double-blind, placebo-controlled studies at 1000 mg, 2000 mg, or 3000 mg/day, given in 2 divided doses, with a treatment duration of up to 18 weeks. In a pooled analysis, the percentage of patients who achieved 50% or greater reduction from baseline in the partial onset seizure frequency per week at stable dose (12/14 weeks) was of 27.7%, 31.6% and 41.3% for patients on 1000, 2000 or 3000 mg levetiracetam respectively and of 12.6% for patients on placebo.

In pediatric patients (4 to 16 years of age), levetiracetam efficacy was established in a double-blind, placebo-controlled study, which included 198 patients and had a treatment duration of 14 weeks. In this study, the patients received levetiracetam as a fixed dose of 60 mg/kg/day (with twice a day dosing).
44.6% of the levetiracetam treated patients and 19.6% of the patients on placebo had a 50% or greater reduction from baseline in the partial onset seizure frequency per week. With continued long-term treatment, 11.4% of the patients were seizure-free for at least 6 months and 7.2% were seizure-free for at least 1 year.

**Monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy.**

Efficacy of levetiracetam as monotherapy was established in a double-blind, parallel group, non-inferiority comparison to carbamazepine controlled release (CR) in 576 patients 16 years of age or older with newly or recently diagnosed epilepsy. The patients had to present with unprovoked partial seizures or with generalized tonic-clonic seizures only. The patients were randomized to carbamazepine CR 400 – 1200 mg/day or levetiracetam 1000 – 3000 mg/day, the duration of the treatment was up to 121 weeks depending on the response.

Six-month seizure freedom was achieved in 73.0% of levetiracetam-treated patients and 72.8% of carbamazepine-CR treated patients; the adjusted absolute difference between treatments was 0.2% (95% CI: -7.8 8.2). More than half of the subjects remained seizure free for 12 months (56.6% and 58.5% of subjects on levetiracetam and on carbamazepine CR respectively).

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

**Adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.**

Levetiracetam efficacy was established in a double-blind, placebo-controlled study of 16 weeks duration, in patients 12 years of age and older suffering from idiopathic generalized epilepsy with myoclonic seizures in different syndromes. The majority of patients presented with juvenile myoclonic epilepsy.

In this study, levetiracetam, dose was 3000 mg/day given in 2 divided doses. 58.3% of the levetiracetam treated patients and 23.3% of the patients on placebo had at least a 50% reduction in myoclonic seizure days per week. With continued long-term treatment, 28.6% of the patients were free of myoclonic seizures for at least 6 months and 21.0% were free of myoclonic seizures for at least 1 year.

**Adjunctive therapy in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalised epilepsy.**

Levetiracetam efficacy was established in a 24-week double-blind, placebo-controlled study which included adults, adolescents and a limited number of children suffering from idiopathic generalized epilepsy with primary generalized tonic-clonic (PGTC) seizures in different syndromes (juvenile myoclonic epilepsy, juvenile absence epilepsy, childhood absence epilepsy, or epilepsy with Grand Mal seizures on awakening). In this study, levetiracetam dose was 3000 mg/day for adults and adolescents or 60 mg/kg/day for children, given in 2 divided doses.

72.2% of the levetiracetam treated patients and 45.2% of the patients on placebo had a 50% or greater decrease in the frequency of PGTC seizures per week. With continued long-term treatment, 47.4% of the patients were free of tonic-clonic seizures for at least 6 months and 31.5% were free of tonic-clonic seizures for at least 1 year.

### 5.2 Pharmacokinetic properties

Levetiracetam is a highly soluble and permeable compound. The pharmacokinetic profile is linear with low intra- and inter-subject variability. There is no modification of the clearance after repeated
administration. There is no evidence for any relevant gender, race or circadian variability. The
pharmacokinetic profile is comparable in healthy volunteers and in patients with epilepsy.

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

A significant correlation between saliva and plasma concentrations has been shown in adults and
children (ratio of saliva/plasma concentrations ranged from 1 to 1.7 for oral tablet formulation and
after 4 hours post-dose for oral solution formulation).

Adults and adolescents

Absorption

Levetiracetam is rapidly absorbed after oral administration. Oral absolute bioavailability is close to
100 %.
Peak plasma concentrations (C_max) are achieved at 1.3 hours after dosing. Steady-state is achieved after
two days of a twice daily administration schedule.
Peak concentrations (C_max) are typically 31 and 43 µg/ml following a single 1,000 mg dose and
repeated 1,000 mg twice daily dose, respectively.
The extent of absorption is dose-independent and is not altered by food.

Distribution

No tissue distribution data are available in humans.
Neither levetiracetam nor its primary metabolite are significantly bound to plasma proteins (< 10 %).
The volume of distribution of levetiracetam is approximately 0.5 to 0.7 l/kg, a value close to the total
body water volume.

Biotransformation

Levetiracetam is not extensively metabolised in humans. The major metabolic pathway (24 % of the
dose) is an enzymatic hydrolysis of the acetamide group. Production of the primary metabolite,
ucb L057, is not supported by liver cytochrome P450 isoforms. Hydrolysis of the acetamide group was
measurable in a large number of tissues including blood cells. The metabolite ucb L057 is
pharmacologically inactive.

Two minor metabolites were also identified. One was obtained by hydroxylation of the pyrrolidone
ring (1.6 % of the dose) and the other one by opening of the pyrrolidone ring (0.9 % of the dose).
Other unidentified components accounted 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 Keppra with other substances, or vice
versa, is unlikely.

Elimination
The plasma half-life in adults was 7±1 hours and did not vary either with dose, route of administration or repeated administration. The mean total body clearance was 0.96 ml/min/kg.

The major route of excretion was via urine, accounting for a mean 95 % of the dose (approximately 93 % of the dose was excreted within 48 hours). Excretion via faeces accounted for only 0.3 % of the dose. The cumulative urinary excretion of levetiracetam and its primary metabolite accounted for 66 % and 24 % of the dose, respectively during the first 48 hours.

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

**Elderly**

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

**Children (4 to 12 years)**

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

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

**Infants and children (1 month to 4 years)**

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

**Renal impairment**

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

In anuric end-stage renal disease adult subjects the half-life was approximately 25 and 3.1 hours during interdialytic and intradialytic periods, respectively. The fractional removal of levetiracetam was 51 % during a typical 4-hour dialysis session.

**Hepatic impairment**

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

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.

In reproductive toxicity studies in the rat, levetiracetam induced developmental toxicity (increase in skeletal variations/minor anomalies, retarded growth, increased pup mortality) at exposure levels similar to or greater than the human exposure. In the rabbit foetal effects (embryonic death, increased skeletal anomalies, and increased malformations) were observed in the presence of maternal toxicity. The systemic exposure at the observed no effect level in the rabbit was about 4 to 5 times the human exposure.

Neonatal and juvenile animal studies in rats and dogs demonstrated that there were no adverse effects seen in any of the standard developmental or maturation endpoints at doses up to 1800 mg/kg/day corresponding to 30 times the maximum recommended human dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate
Citric acid monohydrate
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Ammonium glycyrrhizate
Glycerol (E422)
Maltitol (E965)
Acesulfame potassium (E950)
Grape flavour
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Finished product: 2 years.
After first opening: 2 months

6.4 Special precautions for storage

Store in the original container.

6.5 Nature and contents of container

300 ml amber glass bottle (type III) with a white child resistant closure (polypropylene) in a cardboard box also containing a graduated oral syringe (polyethylene, polystyrene) and a patient information leaflet.
6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/146/027

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 September 2000
Date of last renewal: 08 July 2005

10. DATE OF REVISION OF THE TEXT
1. NAME OF THE MEDICINAL PRODUCT

Keppra 100 mg/ml concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 mg of levetiracetam.
The 5 ml vial contains 500 mg of levetiracetam.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Keppra concentrate is a clear, colorless, sterile solution.

4. CLINICAL PARTICULARS

4.1 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.

Keppra concentrate is an alternative for patients when oral administration is temporarily not feasible.

4.2 Posology and method of administration

Keppra therapy can be initiated with either intravenous or oral administration. Conversion to or from oral to intravenous administration can be done directly without titration. The total daily dose and frequency of administration should be maintained.

Keppra concentrate is for intravenous use only and the recommended dose must be diluted in at least 100 ml of a compatible diluent and administered intravenously as a 15-minute intravenous infusion (see section 6.6).

There is no experience with administration of intravenous levetiracetam for longer period than 4 days.

- 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 (65 years and older)

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.

Dosage recommendations for children and adolescents:

<table>
<thead>
<tr>
<th>Weight</th>
<th>Starting dose: 10 mg/kg twice daily</th>
<th>Maximum dose: 30 mg/kg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 kg  (1)</td>
<td>150 mg twice daily</td>
<td>450 mg twice daily</td>
</tr>
<tr>
<td>20 kg  (1)</td>
<td>200 mg twice daily</td>
<td>600 mg twice daily</td>
</tr>
<tr>
<td>25 kg</td>
<td>250 mg twice daily</td>
<td>750 mg twice daily</td>
</tr>
<tr>
<td>From 50 kg  (2)</td>
<td>500 mg twice daily</td>
<td>1500 mg twice daily</td>
</tr>
</tbody>
</table>

(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.

A Keppra concentrate vial contains 500 mg levetiracetam in 5 ml (corresponding to 100 mg/ml).

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 (see section 5.2).

Patients with renal impairment

The daily dose must be individualised according to renal function.

For adult patients, refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in ml/min is needed. The CLcr in ml/min may be estimated from serum creatinine (mg/dl) determination using the following formula:

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

Then CLcr is adjusted for body surface area (BSA) as follows:

63
\[
\text{CLcr (ml/min)} = \frac{\text{CLcr (ml/min/1.73 m}^2\text{)}}{\text{BSA subject (m}^2\text{)}} \times 1.73
\]

Dosing adjustment for adult patients with impaired renal function

<table>
<thead>
<tr>
<th>Group</th>
<th>Creatinine clearance (ml/min/1.73m(^2))</th>
<th>Dosage and frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt; 80</td>
<td>500 to 1,500 mg twice daily</td>
</tr>
<tr>
<td>Mild</td>
<td>50-79</td>
<td>500 to 1,000 mg twice daily</td>
</tr>
<tr>
<td>Moderate</td>
<td>30-49</td>
<td>250 to 750 mg twice daily</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt; 30</td>
<td>250 to 500 mg twice daily</td>
</tr>
<tr>
<td>End-stage renal disease patients</td>
<td>-</td>
<td>500 to 1,000 mg once daily (2)</td>
</tr>
<tr>
<td>Undergoing dialysis (1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(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.

### 4.3 Contraindications

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

### 4.4 Special warnings and special precautions for use

In accordance with current clinical practice, if Keppra has to be discontinued it is recommended to withdraw it gradually (e.g. in adults: 500 mg 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 section 4.2).
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.

This medicinal product contains 0.313 mmol (or 7.196 mg) of sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Pre-marketing data from clinical studies conducted in adults indicate that Keppra did not influence the serum concentrations of existing antiepileptic medicinal products (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these antiepileptic medicinal products did not influence the pharmacokinetics of Keppra.

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 interaction of levetiracetam with alcohol are available.

4.6 Pregnancy and lactation

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

Levetiracetam is excreted in human breast milk. Therefore, breast-feeding 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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.
Due to possible different individual sensitivity, some patients might experience somnolence or other central nervous system related symptoms, 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.

4.8 Undesirable effects

Undesirable effects that resulted from Keppra intravenous use are similar to those associated with Keppra oral use. The most frequently reported adverse reactions were dizziness, somnolence, headache and postural dizziness. Since there was limited exposure for Keppra intravenous use and since oral and intravenous formulations are bioequivalent, the safety information of Keppra intravenous will rely on Keppra oral use.

In monotherapy 49.8% of the subjects experienced at least one drug related undesirable effect. The most frequently reported undesirable effects were fatigue and somnolence.

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

A study conducted in paediatric patients (4 to 16 years) with partial onset seizures showed that 55.4% of the patients in the Keppra group and 40.2% of the patients in the placebo group experienced undesirable effects. Serious undesirable effects were experienced in 0.0% of the patients in the Keppra group and 1.0% of the patients in the placebo group. The most commonly reported undesirable effects were somnolence, hostility, nervousness, emotional lability, agitation, anorexia, asthenia and headache in the paediatric population. Safety results in paediatric patients were consistent with the safety profile of levetiracetam in adults except for behavioural and psychiatric adverse events which were more common in children than in adults (38.6% versus 18.6%). However, the relative risk was similar in children as compared to adults.

A study conducted in adults and adolescents with myoclonic seizures (12 to 65 years) showed that 33.3% of the patients in the Keppra group and 30.0% of the patients in the placebo group experienced undesirable effects that were judged to be related to treatment. The most commonly reported undesirable effects were headache and somnolence. The incidence of undesirable effects in patients with myoclonic seizures was lower than that in adult patients with partial onset seizures (33.3% versus 46.4%).

A study conducted in adults and children (4 to 65 years) with idiopathic generalised epilepsy with primary generalised tonic-clonic seizures showed that 39.2% of the patients in the Keppra group and 29.8% of the patients in the placebo group experienced undesirable effects that were judged to be related to treatment. The most commonly reported undesirable effect was fatigue.

Undesirable effects reported in clinical studies (adults and children) or from post-marketing experience are listed in the following table per System Organ Class and per frequency. For clinical trials, the frequency is defined as follows: very common (≥1/10); common (≥ 1/100, <1/10); uncommon: (≥ 1/1,000, <1/100); rare (≥ 1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports. Data from post-marketing experience are insufficient to support an estimate of their incidence in the population to be treated.

- General disorders and administration site conditions
  Very common: asthenia/fatigue.
- **Nervous system disorders**
  Very common: somnolence.
  Common: amnesia, ataxia, convulsion, dizziness, headache, hyperkinesia, tremor, balance disorder, disturbance in attention, memory impairment
  Post-marketing experience: paraesthesia

- **Psychiatric disorders**
  Common: agitation, depression, emotional lability/mood swings, hostility/aggression, insomnia, nervousness/irritability, personality disorders, thinking abnormal.
  Post-marketing experience: abnormal behaviour, anger, anxiety, confusion, hallucination, psychotic disorder, suicide, suicide attempt and suicidal ideation.

- **Gastrointestinal disorders**
  Common: abdominal pain, diarrhoea, dyspepsia, nausea, vomiting.
  Post-marketing experience: pancreatitis

- **Hepatobiliary disorders**
  Post-marketing experience: hepatic failure, hepatitis, liver function test abnormal

- **Metabolism and nutrition disorders**
  Common: anorexia, weight increase.
  The risk of anorexia is higher when topiramate is coadministered with levetiracetam.
  Post-marketing experience: weight loss

- **Ear and labyrinth disorders**
  Common: vertigo

- **Eye disorders**
  Common: diplopia, vision blurred

- **Musculoskeletal and connective tissue disorders**
  Common: myalgia

- **Injury, poisoning and procedural complications**
  Common: accidental injury

- **Infections and infestations**
  Common: infection, nasopharyngitis

- **Respiratory, thoracic and mediastinal disorders**
  Common: cough increased

- **Skin and subcutaneous tissue disorders**
  Common: rash, eczema, pruritus
  Post-marketing experience: alopecia: in several cases, recovery was observed when Keppra was discontinued

- **Blood and lymphatic system disorders**
  Common: thrombocytopenia
  Post-marketing experience: leukopenia, neutropenia, pancytopenia (with bone marrow suppression identified in some of the cases).

### 4.9 Overdose
Symptoms

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

Management of overdose

There is no specific antidote for levetiracetam. Treatment of an overdose will be symptomatic and may include haemodialysis. The dialyser extraction efficiency is 60 % for levetiracetam and 74 % for the primary metabolite.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiepileptics, ATC code: N03AX14. The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances.

Mechanism of action

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

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

Clinical experience

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 adults, levetiracetam efficacy has been demonstrated in 3 double-blind, placebo-controlled studies at 1000 mg, 2000 mg, or 3000 mg/day, given in 2 divided doses, with a treatment duration of up to 18 weeks. In a pooled analysis, the percentage of patients who achieved 50% or greater reduction from baseline in the partial onset seizure frequency per week at stable dose (12/14 weeks) was of 27.7%,
31.6% and 41.3% for patients on 1000, 2000 or 3000 mg levetiracetam respectively and of 12.6% for patients on placebo.

In pediatric patients (4 to 16 years of age), levetiracetam efficacy was established in a double-blind, placebo-controlled study, which included 198 patients and had a treatment duration of 14 weeks. In this study, the patients received levetiracetam as a fixed dose of 60 mg/kg/day (with twice a day dosing).

44.6% of the levetiracetam treated patients and 19.6% of the patients on placebo had a 50% or greater reduction from baseline in the partial onset seizure frequency per week. With continued long-term treatment, 11.4% of the patients were seizure-free for at least 6 months and 7.2% were seizure-free for at least 1 year.

**Monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy.**

Efficacy of levetiracetam as monotherapy was established in a double-blind, parallel group, non-inferiority comparison to carbamazepine controlled release (CR) in 576 patients 16 years of age or older with newly or recently diagnosed epilepsy. The patients had to present with unprovoked partial seizures or with generalized tonic-clonic seizures only. The patients were randomized to carbamazepine CR 400 – 1200 mg/day or levetiracetam 1000 – 3000 mg/day, the duration of the treatment was up to 121 weeks depending on the response.

Six-month seizure freedom was achieved in 73.0% of levetiracetam-treated patients and 72.8% of carbamazepine-CR treated patients; the adjusted absolute difference between treatments was 0.2% (95% CI: -7.8 8.2). More than half of the subjects remained seizure free for 12 months (56.6% and 58.5% of subjects on levetiracetam and on carbamazepine CR respectively).

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

**Adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.**

Levetiracetam efficacy was established in a double-blind, placebo-controlled study of 16 weeks duration, in patients 12 years of age and older suffering from idiopathic generalized epilepsy with myoclonic seizures in different syndromes. The majority of patients presented with juvenile myoclonic epilepsy.

In this study, levetiracetam, dose was 3000 mg/day given in 2 divided doses. 58.3% of the levetiracetam treated patients and 23.3% of the patients on placebo had at least a 50% reduction in myoclonic seizure days per week. With continued long-term treatment, 28.6% of the patients were free of myoclonic seizures for at least 6 months and 21.0% were free of myoclonic seizures for at least 1 year.

**Adjunctive therapy in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalised epilepsy.**

Levetiracetam efficacy was established in a 24-week double-blind, placebo-controlled study which included adults, adolescents and a limited number of children suffering from idiopathic generalized epilepsy with primary generalized tonic-clonic (PGTC) seizures in different syndromes (juvenile myoclonic epilepsy, juvenile absence epilepsy, childhood absence epilepsy, or epilepsy with Grand Mal seizures on awakening). In this study, levetiracetam dose was 3000 mg/day for adults and adolescents or 60 mg/kg/day for children, given in 2 divided doses. 72.2% of the levetiracetam treated patients and 45.2% of the patients on placebo had a 50% or greater decrease in the frequency of PGTC seizures per week. With continued long-term treatment, 47.4% of
the patients were free of tonic-clonic seizures for at least 6 months and 31.5% were free of tonic-clonic seizures for at least 1 year.

5.2 Pharmacokinetic properties

The pharmacokinetic profile has been characterized following oral administration. A single dose of 1500 mg levetiracetam diluted in 100 ml of a compatible diluent and infused intravenously over 15 minutes is bioequivalent to 1500 mg levetiracetam oral intake, given as three 500 mg tablets.

The intravenous administration of doses up to 4000 mg diluted in 100 ml of 0.9% sodium chloride infused over 15 minutes and doses up to 2500 mg diluted in 100 ml of 0.9% sodium chloride infused over 5 minutes was evaluated. The pharmacokinetic and safety profiles did not identify any safety concerns.

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. The time independent pharmacokinetic profile of levetiracetam was also confirmed following 1500 mg intravenous infusion for 4 days with b.i.d dosing. 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.

Adults and adolescents

Distribution

Peak plasma concentration (Cmax) observed in 17 subjects following a single intravenous dose of 1500 mg infused over 15 minutes was 51 ± 19 µg/mL (arithmetic average ± standard deviation).

No tissue distribution data are available in humans. Neither levetiracetam nor its primary metabolite are significantly bound to plasma proteins (< 10 %). The volume of distribution of levetiracetam is approximately 0.5 to 0.7 l/kg, a value close to the total body water volume.

Biotransformation

Levetiracetam is not extensively metabolised in humans. The major metabolic pathway (24 % of the dose) is an enzymatic hydrolysis of the acetamide group. Production of the primary metabolite, ucb L057, is not supported by liver cytochrome P450 isoforms. Hydrolysis of the acetamide group was measurable in a large number of tissues including blood cells. The metabolite ucb L057 is pharmacologically inactive.

Two minor metabolites were also identified. One was obtained by hydroxylation of the pyrrolidone ring (1.6 % of the dose) and the other one by opening of the pyrrolidone ring (0.9 % of the dose). Other unidentified components accounted 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 Keppra with other substances, or *vice versa*, is unlikely.

**Elimination**

The plasma half-life in adults was 7±1 hours and did not vary either with dose, route of administration or repeated administration. The mean total body clearance was 0.96 ml/min/kg.

The major route of excretion was via urine, accounting for a mean 95% of the dose (approximately 93% of the dose was excreted within 48 hours). Excretion *via* faeces accounted for only 0.3% of the dose.

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

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

**Elderly**

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

**Children (4 to 12 years)**

The pharmacokinetics in paediatric patients has not been investigated after intravenous administration. However, based on the pharmacokinetic characteristics of levetiracetam, the pharmacokinetics in adults after intravenous administration and the pharmacokinetics in children after oral administration, the exposure (AUC) of levetiracetam is expected to be similar in paediatric patients aged 4 to 12 years after intravenous and oral administration.

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

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

**Renal impairment**

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

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

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

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

5.3 Preclinical safety data

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.

In reproductive toxicity studies in the rat, levetiracetam induced developmental toxicity (increase in skeletal variations/minor anomalies, retarded growth, increased pup mortality) at exposure levels similar to or greater than the human exposure. In the rabbit foetal effects (embryonic death, increased skeletal anomalies, and increased malformations) were observed in the presence of maternal toxicity. The systemic exposure at the observed no effect level in the rabbit was about 4 to 5 times the human exposure.

Neonatal and juvenile animal studies in rats and dogs demonstrated that there were no adverse effects seen in any of the standard developmental or maturation endpoints at doses up to 1800 mg/kg/day corresponding to 30 times the maximum recommended human dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate
Glacial acetic acid
Sodium chloride
Water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Finished product: 2 years.
From a microbiological point of view, the product should be used immediately after dilution. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

No special precautions for storage. For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Keppra concentrate is packed in glass vials (type I) with Teflon faced stoppers and sealed with an aluminium/polypropylene flip off cap. The vials are placed into cartons of 10 vials. Each vial contains 5 ml of concentrate.
6.6 Special precautions for disposal and other handling

One vial of Keppra concentrate contains 500 mg levetiracetam (5 ml concentrate of 100 mg/ml). See Table 1 for the recommended preparation and administration of Keppra concentrate to achieve a total daily dose of 500 mg, 1000 mg, 2000 mg, or 3000 mg in two divided doses.

Table 1. Preparation and administration of Keppra concentrate

<table>
<thead>
<tr>
<th>Dose</th>
<th>Withdrawal Volume</th>
<th>Volume of Diluent</th>
<th>Infusion Time</th>
<th>Frequency of administration</th>
<th>Total Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 mg</td>
<td>2.5 ml (half 5 ml vial)</td>
<td>100 ml</td>
<td>15 minutes</td>
<td>Twice daily</td>
<td>500 mg/day</td>
</tr>
<tr>
<td>500 mg</td>
<td>5 ml (one 5 ml vial)</td>
<td>100 ml</td>
<td>15 minutes</td>
<td>Twice daily</td>
<td>1000 mg/day</td>
</tr>
<tr>
<td>1000 mg</td>
<td>10 ml (two 5 ml vials)</td>
<td>100 ml</td>
<td>15 minutes</td>
<td>Twice daily</td>
<td>2000 mg/day</td>
</tr>
<tr>
<td>1500 mg</td>
<td>15 ml (three 5 ml vials)</td>
<td>100 ml</td>
<td>15 minutes</td>
<td>Twice daily</td>
<td>3000 mg/day</td>
</tr>
</tbody>
</table>

This medicinal product is for single use only, any unused solution should be discarded.

Keppra concentrate was found to be physically compatible and chemically stable when mixed with the following diluents for at least 24 hours and stored in PVC bags at controlled room temperature 15-25°C.

Diluents:
- Sodium chloride (0.9%) injection
- Lactated Ringer’s injection
- Dextrose 5% injection

Product with particulate matter or discoloration should not be used.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/146/030

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 September 2000
Date of last renewal: 08 July 2005

10. DATE OF REVISION OF THE TEXT


ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION
A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Tablets
UCB Pharma SA
Chemin du Foriest
B-1420 Braine l’Alleud
Belgium

Concentrate for solution for infusion
UCB Pharma SA or UCB Pharma S.p.A.
Chemin du Foriest Via Praglia, 15
B-1420 Braine l’Alleud I-10044 Pianezza
Belgium Italy

Oral Solution
NextPharma SAS
17, Route de Meulan
F-78520 Limay
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OF THE MARKETING AUTHORISATION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORIZATION HOLDER

Medicinal product subject to medical prescription.

• CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable

• OTHER CONDITIONS

The MAH will submit PSURs on an annual basis until the next renewal.

Subsequent PSURs will be submitted in accordance to the legislation, unless otherwise specified.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX of 20, 30, 50, 60, 100, 200

1. NAME OF THE MEDICINAL PRODUCT

Keppra 250 mg film-coated tablets
Levetiracetam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 250 mg levetiracetam.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 film-coated tablets
30 film-coated tablets
50 film-coated tablets
60 film-coated tablets
100 film-coated tablets
200 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp : {MM-YYYY}

9. SPECIAL STORAGE CONDITIONS
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder
UCB Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
BELGIUM

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/146/001 20 tablets
EU/1/00/146/002 30 tablets
EU/1/00/146/003 50 tablets
EU/1/00/146/004 60 tablets
EU/1/00/146/005 100 tablets
EU/1/00/146/029 200 tablets

13. BATCH NUMBER

Batch : {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Keppra 250 mg
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Intermediate packaging containing 100 tablets for box of 200 tablets

### 1. NAME OF THE MEDICINAL PRODUCT
Keppra 250 mg film-coated tablets
Levetiracetam

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each film-coated tablet contains 250 mg levetiracetam.

### 3. LIST OF EXCIPIENTS

### 4. PHARMACEUTICAL FORM AND CONTENTS
Film-coated tablets

### 5. METHOD AND ROUTE(S) OF ADMINISTRATION
Oral use
Read the package leaflet before use.

### 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN
Keep out of the reach and sight of children.

### 7. OTHER SPECIAL WARNING(S), IF NECESSARY

### 8. EXPIRY DATE
Exp: {MM-YYYY}

### 9. SPECIAL STORAGE CONDITIONS

### 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder  
UCB Pharma S.A.  
Allée de la Recherche 60  
B-1070 Bruxelles  
BELGIUM

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Batch : {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Keppra 250 mg
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT
Keppra 250 mg film-coated tablets
Levetiracetam

2. NAME OF THE MARKETING AUTHORISATION HOLDER
UCB logo.

3. EXPIRY DATE
Exp : {MM-YYYY}

4. BATCH NUMBER
Batch : {number}

5. OTHER
1. NAME OF THE MEDICINAL PRODUCT

Keppra 500 mg film-coated tablets
Levetiracetam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 500 mg levetiracetam.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

10 film-coated tablets
20 film-coated tablets
30 film-coated tablets
50 film-coated tablets
60 film-coated tablets
100 film-coated tablets
120 film-coated tablets
200 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp : {MM-YYYY}

9. SPECIAL STORAGE CONDITIONS
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder
UCB Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
BELGIUM

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/146/006 10 tablets
EU/1/00/146/007 20 tablets
EU/1/00/146/008 30 tablets
EU/1/00/146/009 50 tablets
EU/1/00/146/010 60 tablets
EU/1/00/146/011 100 tablets
EU/1/00/146/012 120 tablets
EU/1/00/146/013 200 tablets

13. BATCH NUMBER

Batch : {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Keppra 500 mg
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**  
Intermediate packaging containing 100 tablets for box of 200 tablets

1. **NAME OF THE MEDICINAL PRODUCT**

   Keppra 500 mg film-coated tablets  
   Levetiracetam

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

   Each film-coated tablet contains 500 mg levetiracetam.

3. **LIST OF EXCIPIENTS**

4. **PHARMACEUTICAL FORM AND CONTENTS**

   Film-coated tablets

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

   Oral use  
   Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

   Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

   Exp: {MM-YYYY}

9. **SPECIAL STORAGE CONDITIONS**

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**
<table>
<thead>
<tr>
<th>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</th>
</tr>
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<tbody>
<tr>
<td>Marketing Authorisation Holder</td>
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<tr>
<td>UCB Pharma S.A.</td>
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<tr>
<td>Allée de la Recherche 60</td>
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<tr>
<td>B-1070 Bruxelles</td>
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<td>14. GENERAL CLASSIFICATION FOR SUPPLY</td>
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<tr>
<td>Medicinal product subject to medical prescription.</td>
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<tr>
<td>15. INSTRUCTIONS ON USE</td>
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<td></td>
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<tr>
<td>16. INFORMATION IN BRAILLE</td>
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<tr>
<td>Keppra 500 mg</td>
</tr>
<tr>
<td>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</td>
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<tr>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></td>
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<tr>
<td>Keppra 500 mg film-coated tablets</td>
</tr>
<tr>
<td>Levetiracetam</td>
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<td><strong>2. NAME OF THE MARKETING AUTHORISATION HOLDER</strong></td>
</tr>
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<td>UCB logo.</td>
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<td><strong>3. EXPIRY DATE</strong></td>
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<tr>
<td>Exp : {MM-YYYY}</td>
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<tr>
<td><strong>4. BATCH NUMBER</strong></td>
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<tr>
<td>Batch : {number}</td>
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<tr>
<td><strong>5. OTHER</strong></td>
</tr>
</tbody>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Box of 20, 30, 50, 60, 80, 100, 200

1. NAME OF THE MEDICINAL PRODUCT

Keppra 750 mg film-coated tablets
Levetiracetam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 750 mg levetiracetam.

3. LIST OF EXCIPIENTS

Product excipients include E 110. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

20 film-coated tablets
30 film-coated tablets
50 film-coated tablets
60 film-coated tablets
80 film-coated tablets
100 film-coated tablets
200 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp : {MM-YYYY}
9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder
UCB Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
BELGIUM

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/146/014 20 tablets
EU/1/00/146/015 30 tablets
EU/1/00/146/016 50 tablets
EU/1/00/146/017 60 tablets
EU/1/00/146/018 80 tablets
EU/1/00/146/019 100 tablets
EU/1/00/146/028 200 tablets

13. BATCH NUMBER

Batch : {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Keppra 750 mg
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

Intermediate packaging containing 100 tablets for box of 200 tablets

---

1. **NAME OF THE MEDICINAL PRODUCT**

Keppra 750 mg film-coated tablets
Levetiracetam

---

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 750 mg levetiracetam.

---

3. **LIST OF EXCIPIENTS**

Product excipients include E 110. See leaflet for further information.

---

4. **PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablets

---

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use

Read the package leaflet before use.

---

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

---

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

---

8. **EXPIRY DATE**

Exp : {MM-YYYY}

---

9. **SPECIAL STORAGE CONDITIONS**

---

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder
UCB Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
BELGIUM

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Batch: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Keppra 750 mg
# Minimum Particulars to Appear on Blisters or Strips

<table>
<thead>
<tr>
<th>Section</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Name of the Medicinal Product</strong></td>
<td>Keppra 750 mg film-coated tablets</td>
</tr>
<tr>
<td></td>
<td>Levetiracetam</td>
</tr>
<tr>
<td><strong>2. Name of the Marketing Authorisation Holder</strong></td>
<td>UCB logo.</td>
</tr>
<tr>
<td><strong>3. Expiry Date</strong></td>
<td>Exp : {MM-YYYY}</td>
</tr>
<tr>
<td><strong>4. Batch Number</strong></td>
<td>Batch : {number}</td>
</tr>
<tr>
<td><strong>5. Other</strong></td>
<td></td>
</tr>
</tbody>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Box of 10, 20, 30, 50, 60, 100, 200

1. NAME OF THE MEDICINAL PRODUCT
Keppra 1000 mg film-coated tablets
Levetiracetam

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each film-coated tablet contains 1,000 mg levetiracetam.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS
10 film-coated tablets
20 film-coated tablets
30 film-coated tablets
50 film-coated tablets
60 film-coated tablets
100 film-coated tablets
200 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION
Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN
Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE
Exp : {MM-YYYY}

9. SPECIAL STORAGE CONDITIONS
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder
UCB Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
BELGIUM

12. MARKETING AUTHORISATION NUMBER(S)

- EU/1/00/146/020 10 tablets
- EU/1/00/146/021 20 tablets
- EU/1/00/146/022 30 tablets
- EU/1/00/146/023 50 tablets
- EU/1/00/146/024 60 tablets
- EU/1/00/146/025 100 tablets
- EU/1/00/146/026 200 tablets

13. BATCH NUMBER

Batch : {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Keppra 1000 mg
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Intermediate packaging containing 100 tablets for box of 200 tablets

### 1. NAME OF THE MEDICINAL PRODUCT

Keppra 1000 mg film-coated tablets  
Levetiracetam

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

### 3. LIST OF EXCIPIENTS

### 4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

### 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

### 7. OTHER SPECIAL WARNING(S), IF NECESSARY

### 8. EXPIRY DATE

Exp : {MM-YYYY}

### 9. SPECIAL STORAGE CONDITIONS

### 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Marketing Authorisation Holder
UCB Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
BELGIUM

12. **MARKETING AUTHORISATION NUMBER(S)**

13. **BATCH NUMBER**

Batch : {number}

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Keppra 1000 mg
# MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

<p>| | |</p>
<table>
<thead>
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<tbody>
<tr>
<td>1.</td>
<td><strong>NAME OF THE MEDICINAL PRODUCT</strong></td>
</tr>
<tr>
<td></td>
<td>Keppra 1000 mg film-coated tablets</td>
</tr>
<tr>
<td></td>
<td>Levetiracetam</td>
</tr>
<tr>
<td>2.</td>
<td><strong>NAME OF THE MARKETING AUTHORISATION HOLDER</strong></td>
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<tr>
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<td>UCB logo.</td>
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<td>3.</td>
<td><strong>EXPIRY DATE</strong></td>
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<td>4.</td>
<td><strong>BATCH NUMBER</strong></td>
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<td>Batch : {number}</td>
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<tr>
<td>5.</td>
<td><strong>OTHER</strong></td>
</tr>
</tbody>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND ON THE IMMEDIATE PACKAGING

BOTTLE of 300 ml

1. NAME OF THE MEDICINAL PRODUCT

Keppra 100 mg/ml oral solution
Levetiracetam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 mg levetiracetam.

3. LIST OF EXCIPIENTS

Other ingredients include E216, E218 and maltitol. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution. Bottle of 300 ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp : {MM-YYYY}
Do not use after 2 months of first opening the bottle

9. SPECIAL STORAGE CONDITIONS

Store in the original container.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORITY

Marketing Authorisation Holder
UCB Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
BELGIUM

12. MARKETING AUTHORITY NUMBER(S)

EU/1/00/146/027

13. BATCH NUMBER

Batch : {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Keppra 100 mg/ml
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

| Box of 10 vials |

---

**1. NAME OF THE MEDICINAL PRODUCT**

Keppra 100 mg/ml concentrate for solution for infusion  
Levetiracetam

---

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One vial contains 500 mg/5 ml levetiracetam.

---

**3. LIST OF EXCIPIENTS**

Other ingredients include sodium acetate, glacial acetic acid, sodium chloride, water for injection

---

**4. PHARMACEUTICAL FORM AND CONTENTS**

10 vials of concentrate for solution for infusion

---

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Intravenous use

Read the package leaflet before use.

---

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

---

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

---

**8. EXPIRY DATE**

EXP : {MM-YYYY}  
Use immediately after dilution.

---

**9. SPECIAL STORAGE CONDITIONS**

---

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

---
11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Marketing Authorisation Holder  
UCB Pharma S.A.  
Allée de la Recherche 60  
B-1070 Bruxelles  
BELGIUM

12. **MARKETING AUTHORISATION NUMBER(S)**

EU/1/00/146/030

13. **BATCH NUMBER**

Batch : {number}

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
vial of 5 ml

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Keppra 100 mg/ml concentrate for solution for infusion
Levetiracetam
Intravenous administration

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP : {MM-YYYY}
Use immediately after dilution.

4. BATCH NUMBER

Batch : {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

500 mg/5 ml

6. OTHER
B. PACKAGE LEAFLET
Read all of this leaflet carefully before you start taking this medicine.

− Keep this leaflet. You may need to read it again.
− If you have any further questions, ask your doctor or pharmacist.
− This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
− 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.

In this leaflet:
1. What Keppra is and what it is used for
2. Before you take Keppra
3. How to take Keppra
4. Possible side effects
5. How to store Keppra
6. Further information

1. WHAT KEPPRA IS AND WHAT IT IS USED FOR

Keppra 250 mg film-coated tablets is an antiepileptic medicine (a medicine used to treat seizures in epilepsy).

Keppra is used alone in the treatment of partial seizures in patients from 16 years of age.

Keppra is used in patients who are already taking another antiepileptic medicine

- in the treatment of partial seizures in adults and children from 4 years age
- in the treatment of myoclonic seizures in patients 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

2. BEFORE YOU TAKE KEPPRA

Keppra is used in adults and children over 4 years of age. It is not recommended for children less than 4 years old.

Do not take Keppra:
- if you are allergic (hypersensitive) to levetiracetam or any of the other ingredients of Keppra.

Take special care with Keppra:
- if you suffer from kidney problems, follow your doctor’s instructions. He/she may decide if your dose should be adjusted.
- No impact on growth and puberty were noticed in children who have taken Keppra. However, there is limited experience on long term effects in children.
- If you notice an increase in seizure severity (e.g. increased number), please contact your doctor.
- If you have any symptoms of depression and/or suicidal ideation, please contact your doctor.

Taking other medicines:
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
Taking Keppra with food and drink:
You may take Keppra with or without food. As a safety precaution, do not take Keppra with alcohol.

Pregnancy and breast-feeding:
Ask your doctor or pharmacist for advice before taking any medicine.
If you are pregnant or if you think you may be pregnant, please inform your doctor.
Keppra should not be used during pregnancy unless clearly necessary. The potential risk to your unborn child is unknown. Keppra has shown unwanted reproductive effects in animal studies at dose levels higher than you would need to control your seizures.
Breast-feeding is not recommended during treatment.

Driving and using machines:
Keppra may impair your ability to drive or operate any tools or machinery, as Keppra may make you feel sleepy. This is more likely at the beginning of treatment or after an increase in the dose. You should not drive or use machines until it is established that your ability to perform such activities is not affected.

3. HOW TO TAKE KEPPRA

Dosage in adults and adolescents (12 to 17 years) weighing 50 kg or more:
Take the number of tablets following your doctor’s instructions.
• General dose: between 1,000 mg (4 tablets) and 3,000 mg (12 tablets) each day.
• Keppra must be taken twice a day, once in the morning and once in the evening, at about the same time each day.
Example: if your daily dose is 1,000 mg, you must take 2 tablets in the morning and 2 tablets in the evening.

Dosage in children (4 to 11 years) and adolescents (12 to 17 years) weighing less than 50 kg:
Give to your child the number of tablets following your doctor’s instructions.
• General dose: between 20 mg/kg and 60 mg/kg each day.
• Keppra must be taken twice a day, once in the morning and once in the evening, at about the same time each day.

Administration:
Swallow Keppra tablets with a sufficient quantity of liquid (e.g. a glass of water).

Duration of treatment:
• Keppra is used as a chronic treatment. You should continue Keppra treatment for as long as your doctor has told you.
• Do not stop your treatment without your doctor’s advice as this could increase your seizures. Should your doctor decide to stop your Keppra treatment, he/she will instruct you about the gradual withdrawal of Keppra.

If you take more Keppra than you should:
Contact your doctor if you took more tablets than you should.

If you forget to take Keppra:
Contact your doctor if you have missed one or more doses.
Do not take a double dose to make up for a forgotten tablet.

If you stop taking Keppra:
If stopping treatment, as with other antiepileptic medicines, Keppra should be discontinued gradually to avoid an increase of seizures.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE 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;
- 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.

5. HOW TO STORE KEPPRA

- Keep out of the reach and sight of children.
- This medicinal product does not require any special storage conditions.

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

The expiry date refers to the last day of the month.

6. FURTHER INFORMATION
What Keppra contains

- The active substance is called levetiracetam.
- The other ingredients are:
  
  Tablet core: Sodium croscarmellose, Macrogol 6000, Colloidal anhydrous silica, Magnesium stearate.
  
  Film-coating: Opadry 85F20694 (Polyvinyl alcohol-part. hydrolyzed, Titanium dioxide (E171), Macrogol 3350, Talc, Indigo carmine aluminium lake (E132)).

Keppra film-coated tablets are packed in blisters in cardboard boxes. Each tablet contains 250 mg of levetiracetam.

What Keppra looks like and contents of the pack

The film-coated tablets are blue, oblong, scored and debossed with the code “ucb” and “250” on one side.

The cardboard boxes contain 20, 30, 50, 60, 100 and 200 film-coated tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: UCB Pharma S.A., Allée de la Recherche 60, B-1070 Bruxelles, Belgium.

Manufacturer: UCB Pharma SA, Chemin du Foriest, B-1420 Braine-l’Alleud, Belgium.

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This leaflet was last approved on {date}

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu
Read all of this leaflet carefully before you start taking this medicine.

− Keep this leaflet. You may need to read it again.
− If you have any further questions, ask your doctor or pharmacist.
− This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
− 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.

In this leaflet:
1. What Keppra is and what it is used for
2. Before you take Keppra
3. How to take Keppra
4. Possible side effects
5. How to store Keppra
6. Further information

1. WHAT KEPPRA IS AND WHAT IT IS USED FOR

Keppra 500 mg film-coated tablets is an antiepileptic medicine (a medicine used to treat seizures in epilepsy).

Keppra is used alone in the treatment of partial seizures in patients from 16 years of age

Keppra is used in patients who are already taking another antiepileptic medicine.

- in the treatment of partial seizures in adults and children from 4 years age
- in the treatment of myoclonic seizures in patients 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

2. BEFORE YOU TAKE KEPPRA

Keppra is used in adults and children over 4 years of age. It is not recommended for children less than 4 years old.

Do not take Keppra:
- if you are allergic (hypersensitive) to levetiracetam or any of the other ingredients of Keppra.

Take special care with Keppra:
- if you suffer from kidney problems, follow your doctor’s instructions. He/she may decide if your dose should be adjusted.
- No impact on growth and puberty were noticed in children who have taken Keppra. However, there is limited experience on long term effects in children.
- If you notice an increase in seizure severity (e.g. increased number), please contact your doctor.
- If you have any symptoms of depression and/or suicidal ideation, please contact your doctor.

Taking other medicines:
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

**Taking Keppra with food and drink:**
You may take Keppra with or without food. As a safety precaution, do not take Keppra with alcohol.

**Pregnancy and breast-feeding:**
Ask your doctor or pharmacist for advice before taking any medicine. If you are pregnant or if you think you may be pregnant, please inform your doctor. Keppra should not be used during pregnancy unless clearly necessary. The potential risk to your unborn child is unknown. Keppra has shown unwanted reproductive effects in animal studies at dose levels higher than you would need to control your seizures. Breast-feeding is not recommended during treatment.

**Driving and using machines:**
Keppra may impair your ability to drive or operate any tools or machinery, as Keppra may make you feel sleepy. This is more likely at the beginning of treatment or after an increase in the dose. You should not drive or use machines until it is established that your ability to perform such activities is not affected.

3. **HOW TO TAKE KEPPRA**

**Dosage in adults and adolescents (12 to 17 years) weighing 50 kg or more:**
Take the number of tablets following your doctor’s instructions.
- General dose: between 1,000 mg (2 tablets) and 3,000 mg (6 tablets) each day.
- Keppra must be taken twice a day, once in the morning and once in the evening, at about the same time each day.

*Example: if your daily dose is 1,000 mg, you must take one tablet in the morning and one tablet in the evening.*

**Dosage in children (4 to 11 years) and adolescents (12 to 17 years) weighing less than 50 kg:**
Give to your child the number of tablets following your doctor’s instructions.
- General dose: between 20 mg/kg and 60 mg/kg each day.
- Keppra must be taken twice a day, once in the morning and once in the evening, at about the same time each day.

Keppra 100 mg/ml oral solution and Keppra 250 mg tablets are presentations more appropriate to young children.

**Administration:**
Swallow Keppra tablets with a sufficient quantity of liquid (e.g., a glass of water).

**Duration of treatment:**
- Keppra is used as a chronic treatment. You should continue Keppra treatment for as long as your doctor has told you.
- Do not stop your treatment without your doctor’s advice as this could increase your seizures. Should your doctor decide to stop your Keppra treatment, he/she will instruct you about the gradual withdrawal of Keppra.

**If you take more Keppra than you should:**
Contact your doctor if you took more tablets than you should.

**If you forget to take Keppra:**
Contact your doctor if you have missed one or more doses. Do not take a double dose to make up for a forgotten tablet.
If you stop taking Keppra:
If stopping treatment, as with other antiepileptic medicines, Keppra should be discontinued gradually
to avoid an increase of seizures.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE 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;
- 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.

5. HOW TO STORE KEPPRA

- Keep out of the reach and sight of children.
- This medicinal product does not require any special storage conditions.

Do not use after the expiry date stated on the carton box and blister after EXP:.
The expiry date refers to the last day of the month.
6. FURTHER INFORMATION

What Keppra contains

• The active substance is called levetiracetam.
  The other ingredients are:
  Tablet core: Sodium croscarmellose, Macrogol 6000, Colloidal anhydrous silica, Magnesium stearate.
  Film-coating: Opadry 85F32004 (Polyvinyl alcohol-part. hydrolyzed, Titanium dioxide (E171),
              Macrogol 3350, Talc, Iron oxide yellow (E172)).

Keppra film-coated tablets are packed in blisters in cardboard boxes. Each tablet contains 500 mg of levetiracetam.

What Keppra looks like and contents of the pack

The film-coated tablets are yellow, oblong, scored and debossed with the code “ucb” and “500” on one side.
The cardboard boxes contain 10, 20, 30, 50, 60, 100, 120 and 200 film-coated tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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Manufacturer: UCB Pharma SA, Chemin du Foriest, B-1420 Braine-l’Alleud, Belgium.

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This leaflet was last approved on {date}

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu
Keppra 750 mg film-coated tablets
Levetiracetam

Read all of this leaflet carefully before you start taking this medicine.
– Keep this leaflet. You may need to read it again.
– If you have any further questions, ask your doctor or pharmacist.
– This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
– 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.

In this leaflet:
1. What Keppra is and what it is used for
2. Before you take Keppra
3. How to take Keppra
4. Possible side effects
5. How to store Keppra
6. Further information

1. WHAT KEPPRA IS AND WHAT IT IS USED FOR

Keppra 750 mg film-coated tablets is an antiepileptic medicine (a medicine used to treat seizures in epilepsy).

Keppra is used alone in the treatment of partial seizures in patients from 16 years of age

Keppra is used in patients who are already taking another antiepileptic medicine
• in the treatment of partial seizures in adults and children from 4 years age
• in the treatment of myoclonic seizures in patients 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

2. BEFORE YOU TAKE KEPPRA

Keppra is used in adults and children over 4 years of age. It is not recommended for children less than 4 years old.

Do not take Keppra:
• if you are allergic (hypersensitive) to levetiracetam or any of the other ingredients of Keppra.

Take special care with Keppra:
• if you suffer from kidney problems, follow your doctor’s instructions. He/she may decide if your dose should be adjusted.
• No impact on growth and puberty were noticed in children who have taken Keppra. However, there is limited experience on long term effects in children.
• If you notice an increase in seizure severity (e.g. increased number), please contact your doctor.
• If you have any symptoms of depression and/or suicidal ideation, please contact your doctor.

Taking other medicines:
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

**Taking Keppra with food and drink:**
You may take Keppra with or without food. As a safety precaution, do not take Keppra with alcohol.

**Pregnancy and breast-feeding:**
Ask your doctor or pharmacist for advice before taking any medicine. If you are pregnant or if you think you may be pregnant, please inform your doctor. Keppra should not be used during pregnancy unless clearly necessary. The potential risk to your unborn child is unknown. Keppra has shown unwanted reproductive effects in animal studies at dose levels higher than you would need to control your seizures. Breast-feeding is not recommended during treatment.

**Driving and using machines:**
Keppra may impair your ability to drive or operate any tools or machinery, as Keppra may make you feel sleepy. This is more likely at the beginning of treatment or after an increase in the dose. You should not drive or use machines until it is established that your ability to perform such activities is not affected.

**Important information about some of the ingredients of Keppra:**
E 110 coloring agent may cause allergic reactions.

### 3. HOW TO TAKE KEPPRA

**Dosage in adults and adolescents (12 to 17 years) weighing 50 kg or more:**
Take the number of tablets following your doctor’s instructions.
- General dose: between 1,000 mg and 3,000 mg each day.
- Keppra must be taken twice a day, once in the morning and once in the evening, at about the same time each day.

*Example: if your daily dose is 1,500 mg, you must take one tablet in the morning and one tablet in the evening.*

**Dosage in children (4 to 11 years) and adolescents (12 to 17 years) weighing less than 50 kg:**
Give to your child the number of tablets following your doctor’s instructions.
- General dose: between 20 mg/kg and 60 mg/kg each day.
- Keppra must be taken twice a day, once in the morning and once in the evening, at about the same time each day.

Keppra 100 mg/ml oral solution and Keppra 250 mg tablets are presentations more appropriate to young children.

**Administration:**
Swallow Keppra tablets with a sufficient quantity of liquid (*e.g.* a glass of water).

**Duration of treatment:**
- Keppra is used as a chronic treatment. You should continue Keppra treatment for as long as your doctor has told you.
- **Do not stop your treatment without your doctor’s advice as this could increase your seizures.** Should your doctor decide to stop your Keppra treatment, he/she will instruct you about the gradual withdrawal of Keppra.

**If you take more Keppra than you should:**
Contact your doctor if you took more tablets than you should.

**If you forget to take Keppra:**
Contact your doctor if you have missed one or more doses. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Keppra:
If stopping treatment, as with other antiepileptic medicines, Keppra should be discontinued gradually to avoid an increase of seizures.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE 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;
- 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.

5. HOW TO STORE KEPPRA
- Keep out of the reach and sight of children.
- This medicinal product does not require any special storage conditions.
Do not use after the expiry date stated on the carton box and blister after EXP:.
The expiry date refers to the last day of the month.

6. FURTHER INFORMATION

What Keppra contains
- The active substance is called levetiracetam.
The other ingredients are:
  Tablet core: Sodium croscarmellose, Macrogol 6000, Colloidal anhydrous silica, Magnesium stearate.
  Film-coating: Opadry 85F23452 (Polyvinyl alcohol-part. hydrolyzed, Titanium dioxide (E171), Macrogol 3350, Talc, sunset yellow FCF aluminium lake (E110), Iron oxide red (E172)).

Keppra film-coated tablets are packed in blisters in cardboard boxes. Each tablet contains 750 mg of levetiracetam.

What Keppra looks like and contents of the pack
The film-coated tablets are orange, oblong, scored and debossed with the code “ucb” and “750” on one side.
The cardboard boxes contain 20, 30, 50, 60, 80, 100 and 200 film-coated tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
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Manufacturer: UCB Pharma SA, Chemin du Foriest, B-1420 Braine-l’Alleud, Belgium.

Local representatives
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<tr>
<th>Country</th>
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Detailed information on this medicine is available on the European Medicines Agency (EMEA) website: http://www.emea.europa.eu
Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- 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.

In this leaflet:
1. What Keppra is and what it is used for
2. Before you take Keppra
3. How to take Keppra
4. Possible side effects
5. How to store Keppra
6. Further information

1. WHAT KEPPRA IS AND WHAT IT IS USED FOR

Keppra 1000 mg film-coated tablets is an antiepileptic medicine (a medicine used to treat seizures in epilepsy).

Keppra is used alone in the treatment of partial seizures in patients from 16 years of age.

Keppra is used in patients who are already taking another antiepileptic medicine
- in the treatment of partial seizures in adults and children from 4 years of age
- in the treatment of myoclonic seizures in patients 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

2. BEFORE YOU TAKE KEPPRA

Keppra is used in adults and children over 4 years of age. It is not recommended for children less than 4 years old.

Do not take Keppra:
- if you are allergic (hypersensitive) to levetiracetam or any of the other ingredients of Keppra.

Take special care with Keppra:
- if you suffer from kidney problems, follow your doctor’s instructions. He/she may decide if your dose should be adjusted.
- No impact on growth and puberty were noticed in children who have taken Keppra. However, there is limited experience on long term effects in children.
- If you notice an increase in seizure severity (e.g. increased number), please contact your doctor.
- If you have any symptoms of depression and/or suicidal ideation, please contact your doctor.

Taking other medicines:
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Keppra with food and drink:
You may take Keppra with or without food. As a safety precaution, do not take Keppra with alcohol.

Pregnancy and breast-feeding:
Ask your doctor or pharmacist for advice before taking any medicine.
If you are pregnant or if you think you may be pregnant, please inform your doctor.
Keppra should not be used during pregnancy unless clearly necessary. The potential risk to your unborn child is unknown. Keppra has shown unwanted reproductive effects in animal studies at dose levels higher than you would need to control your seizures.
Breast-feeding is not recommended during treatment.

Driving and using machines:
Keppra may impair your ability to drive or operate any tools or machinery, as Keppra may make you feel sleepy. This is more likely at the beginning of treatment or after an increase in the dose. You should not drive or use machines until it is established that your ability to perform such activities is not affected.

3. HOW TO TAKE KEPPRA

Dosage in adults and adolescents (12 to 17 years) weighing 50 kg or more:
Take the number of tablets following your doctor’s instructions.
- General dose: between 1,000 mg and 3,000 mg each day.
- Keppra must be taken twice a day, once in the morning and once in the evening, at about the same time each day.
Example: if your daily dose is 2,000 mg, you must take one tablet in the morning and one tablet in the evening.

Dosage in children (4 to 11 years) and adolescents (12 to 17 years) weighing less than 50 kg:
Give to your child the number of tablets following your doctor’s instructions.
- General dose: between 20 mg/kg and 60 mg/kg each day.
- Keppra must be taken twice a day, once in the morning and once in the evening, at about the same time each day.
Keppra 100 mg/ml oral solution and Keppra 250 mg tablets are presentations more appropriate to young children.

Administration:
Swallow Keppra tablets with a sufficient quantity of liquid (e.g. a glass of water).

Duration of treatment:
- Keppra is used as a chronic treatment. You should continue Keppra treatment for as long as your doctor has told you.
- Do not stop your treatment without your doctor’s advice as this could increase your seizures. Should your doctor decide to stop your Keppra treatment, he/she will instruct you about the gradual withdrawal of Keppra.

If you take more Keppra than you should:
Contact your doctor if you took more tablets than you should.

If you forget to take Keppra:
Contact your doctor if you have missed one or more doses.
Do not take a double dose to make up for a forgotten tablet.
If you stop taking Keppra:
If stopping treatment, as with other antiepileptic medicines, Keppra should be discontinued gradually to avoid an increase of seizures.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE 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 disorders (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;
- 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.

5. HOW TO STORE KEPPRA

- Keep out of the reach and sight of children.
- This medicinal product does not require any special storage conditions.

Do not use after the expiry date stated on the carton box and blister after EXP:. The expiry date refers to the last day of the month.
6. FURTHER INFORMATION

What Keppra contains
- The active substance is called levetiracetam.
- The other ingredients are:
  Tablet core: Sodium croscarmellose, Macrogol 6000, Colloidal anhydrous silica, Magnesium stearate.
  Film-coating: Opadry 85F18422 (Polyvinyl alcohol-part. hydrolyzed, Titanium dioxide (E171), Macrogol 3350, Talc).

Keppra film-coated tablets are packed in blisters in cardboard boxes. Each tablet contains 1,000 mg of levetiracetam.

What Keppra looks like and contents of the pack
The film-coated tablets are white, oblong, scored and debossed with the code “ucb” and “1000” on one side.
The cardboard boxes contain 10, 20, 30, 50, 60, 100 and 200 film-coated tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder: UCB Pharma S.A., Allée de la Recherche 60, B-1070 Bruxelles, Belgium.
Manufacturer: UCB Pharma SA, Chemin du Foriest, B-1420 Braine-l’Alleud, Belgium.

Local representatives
For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu
**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**Keppra 100 mg/ml oral solution**
Levetiracetam

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- 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.

**In this leaflet:**
1. What Keppra is and what it is used for
2. Before you take Keppra
3. How to take Keppra
4. Possible side effects
5. How to store Keppra
6. Further information

**1. WHAT KEPPRA IS AND WHAT IT IS USED FOR**

Keppra 100 mg/ml oral solution is an antiepileptic medicine (a medicine used to treat seizures in epilepsy).

Keppra is used alone for the treatment of partial seizures in patients from 16 years of age.

Keppra is used in patients who are already taking another antiepileptic medicine
- in the treatment of partial seizures in adults and children from 4 years age
- in the treatment of myoclonic seizures in patients 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

**2. BEFORE YOU TAKE KEPPRA**

Keppra is used in adults and children over 4 years of age. It is not recommended for children less than 4 years old.

**Do not take Keppra:**
- if you are allergic (hypersensitive) to levetiracetam or any of the other ingredients of Keppra.

**Take special care with Keppra:**
- if you suffer from kidney problems, follow your doctor’s instructions. He/she may decide if your dose should be adjusted.
- No impact on growth and puberty were noticed in children who have taken Keppra. However, there is limited experience on long term effects in children.
- If you notice an increase in seizure severity (e.g. increased number), please contact your doctor.
- If you have any symptoms of depression and/or suicidal ideation, please contact your doctor.

**Taking other medicines:**
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

**Taking Keppra with food and drink:**
You may take Keppra with or without food. As a safety precaution, do not take Keppra with alcohol.

**Pregnancy and breast-feeding:**
Ask your doctor or pharmacist for advice before taking any medicine. If you are pregnant or if you think you may be pregnant, please inform your doctor. Keppra should not be used during pregnancy unless clearly necessary. The potential risk to your unborn child is unknown. Keppra has shown unwanted reproductive effects in animal studies at dose levels higher than you would need to control your seizures. Breast-feeding is not recommended during treatment.

**Driving and using machines:**
Keppra may impair your ability to drive or operate any tools or machinery, as Keppra may make you feel sleepy. This is more likely at the beginning of treatment or after an increase in the dose. You should not drive or use machines until it is established that your ability to perform such activities is not affected.

**Important information about some of the ingredients of Keppra:**
Keppra oral solution includes methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) which may cause allergic reactions (possibly delayed). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

### 3. HOW TO TAKE KEPPRA

**Dosage in adults and adolescents (12 to 17 years) weighing 50 kg or more:**
Take the oral solution following your doctor’s instructions.
- General dose: between 1,000 mg (10 ml) and 3,000 mg (30 ml) each day.
- Keppra must be taken twice a day, once in the morning and once in the evening, at about the same time each day.

*Example: if your daily dose is 1,000 mg, you must take 500 mg (equal to 5 ml) in the morning and 500 mg (equal to 5 ml) in the evening.*

**Dosage in children (4 to 11 years) and adolescents (12 to 17 years) weighing less than 50 kg:**
Give to your child the amount of oral solution following your doctor’s instructions.
- General dose: between 20 mg/kg and 60 mg/kg each day.
- Keppra must be taken twice a day, once in the morning and once in the evening, at about the same time each day.

*Example: for a general dose of 20 mg/kg each day, you must give your 15 kg child 150 mg (equal to 1.5 ml) in the morning and 150 mg (equal to 1.5 ml) in the evening.*

**Administration:**
Keppra oral solution may be diluted in a glass of water.
Instruction for use:
- Open the bottle: press the cap and turn it anticlockwise (figure ①)
- Take the syringe and put it in the bottle (figure ②)
- Fill the syringe with the liquid by pulling the piston up to the graduation mark corresponding to the quantity in milligrams (mg) prescribed by your doctor (figure ③)
- Remove the syringe from the bottle (figure ④)
- Empty the contents of the syringe in a glass of water by pushing the piston to the bottom (figure ⑤)
- Drink the whole contents of the glass
• Wash the syringe with water (figure ©)
Close the bottle with the plastic screw cap.

Duration of treatment:
- Keppra is used as a chronic treatment. You should continue Keppra treatment for as long as your doctor has told you.
- Do not stop your treatment without your doctor’s advice as this could increase your seizures. Should your doctor decide to stop your Keppra treatment, he/she will instruct you about the gradual withdrawal of Keppra.

If you take more Keppra than you should:
Contact your doctor if you took more Keppra than you should.

If you forget to take Keppra:
Contact your doctor if you have missed one or more doses. Do not take a double dose to make up for a forgotten dose.

If you stop taking Keppra:
If stopping treatment, as with other antiepileptic medicines, Keppra should be discontinued gradually to avoid an increase of seizures.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE 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;
• 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.

5. HOW TO STORE KEPPRA

• Keep out of the reach and sight of children.
• Due to sensitivity to light, store in the original container.

Do not use after the expiry date stated on the cardboard box and bottle after EXP:.
The expiry date refers to the last day of the month.
Do not use after 2 months of first opening the bottle.

6. FURTHER INFORMATION

What Keppra contains
• The active substance is called levetiracetam.
• The other ingredients are: sodium citrate, Citric acid monohydrate, Methyl
parahydroxybenzoate (E218), Propyl parahydroxybenzoate (E216), Ammonium glycyrrhizate,
Glycerol (E422), Maltitol (E965), Acesulfame potassium (E950), Grape flavour, Purified water.

Keppra is packed in a 300 ml glass bottle in a cardboard box. Each ml contains 100 mg of
levetiracetam.

What Keppra looks like and contents of the pack
Keppra 100 mg/ml oral solution is a clear liquid.
The 300 ml glass bottle of Keppra is packed in a cardboard box containing a graduated oral syringe.
Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder: UCB Pharma S.A., Allée de la Recherche 60, B-1070 Bruxelles, Belgium.
Manufacturer: NextPharma SAS, 17 Route de Meulan, F-78520 Limay, France.

Local representatives
For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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Read all of this leaflet carefully before you start using this medicine.
– Keep this leaflet. You may need to read it again.
– If you have any further questions, ask your doctor or pharmacist.
– This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
– 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.

In this leaflet:
1. What Keppra is and what it is used for
2. Before you use Keppra
3. How to use Keppra
4. Possible side effects
5. How to store Keppra
6. Further information

1. WHAT KEPPRA IS AND WHAT IT IS USED FOR

Keppra concentrate is an antiepileptic medicine (a medicine used to treat seizures in epilepsy).

Keppra is used alone in the treatment of partial seizures in patients from 16 years of age,

Keppra is used in patients who are already taking another antiepileptic medicine
• in the treatment of partial seizures in adults and children from 4 years age
• in the treatment of myoclonic seizures in patients 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

Keppra concentrate is an alternative for patients when administration of the antiepileptic oral Keppra medicine is temporarily not feasible.

2. BEFORE YOU USE KEPPRA

Keppra is used in adults and children over 4 years of age. It is not recommended for children less than 4 years old.

Do not use Keppra:
• if you are allergic (hypersensitive) to levetiracetam or any of the other ingredients of Keppra.

Take special care with Keppra:
• if you suffer from kidney problems, follow your doctor’s instructions. He/she may decide if your dose should be adjusted.
• No impact on growth and puberty were noticed in children who have taken Keppra. However, there is limited experience on long term effects in children.
• If you notice an increase in seizure severity (e.g. increased number), please contact your doctor.
• If you have any symptoms of depression and/or suicidal ideation, please contact your doctor.
Taking other medicines:
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Using Keppra with food and drink:
You may take Keppra with or without food. As a safety precaution, do not use Keppra with alcohol.

Pregnancy and breast-feeding:
Ask your doctor or pharmacist for advice before taking any medicine.
If you are pregnant or if you think you may be pregnant, please inform your doctor.
Keppra should not be used during pregnancy unless clearly necessary. The potential risk to your unborn child is unknown. Keppra has shown unwanted reproductive effects in animal studies at dose levels higher than you would need to control your seizures.
Breast-feeding is not recommended during treatment.

Driving and using machines:
Keppra may impair your ability to drive or operate any tools or machinery, as Keppra may make you feel sleepy. This is more likely at the beginning of treatment or after an increase in the dose. You should not drive or use machines until it is established that your ability to perform such activities is not affected.

Important information about some of the ingredients of Keppra
Other ingredients include sodium acetate, glacial acetic acid, sodium chloride, water for injection

One vial of Keppra concentrate contains 0.313 mmol (or 7.196 mg) of sodium. This should be taken into consideration if you are on a controlled sodium diet.

3. HOW TO USE KEPPRA

The intravenous formulation is an alternative to your oral administration. Conversion to or from oral to intravenous administration can be done directly without titration. Your total daily dose and frequency of administration remain identical.

Dosage in adults and adolescents (12 to 17 years) weighing 50 kg or more:
- General dose: between 1,000 mg and 3,000 mg each day.
- Keppra must be administered twice a day, once in the morning and once in the evening, at about the same time each day.

Dosage in children (4 to 11 years) and adolescents (12 to 17 years) weighing less than 50 kg:
- General dose: between 20 mg/kg and 60 mg/kg each day.
- Keppra must be administered twice a day, once in the morning and once in the evening, at about the same time each day.

Method and route of administration:
Keppra is administered as an intravenous infusion by a healthcare professional.
Keppra will be diluted in at least 100 ml of a compatible diluent and infused over 15-minutes.
For medical or healthcare professionals, more detailed direction for the proper use of Keppra is provided in section 6.

Duration of treatment:
- Keppra is used as a chronic treatment. You should continue Keppra treatment for as long as your doctor has told you.
Do not stop your treatment without your doctor’s advice as this could increase your seizures. Should your doctor decide to stop your Keppra treatment, he/she will instruct you about the gradual withdrawal of Keppra.

There is no experience with administration of intravenous levetiracetam for a longer period than 4 days.

If you stop using Keppra:
If stopping treatment, as with other antiepileptic medicines, Keppra should be discontinued gradually to avoid an increase of seizures.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE 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;
• 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.
5. **HOW TO STORE KEPPRA**

- Keep out of the reach and sight of children.
- This medicinal product does not require any special storage conditions.

Do not use after the expiry date stated on the vial and carton box after EXP: The expiry date refers to the last day of the month.

6. **FURTHER INFORMATION**

**What Keppra contains**

- The active substance is called levetiracetam.
- The other ingredients are: sodium acetate, glacial acetic acid, sodium chloride, water for injection

Keppra concentrate is contained in a 5 ml glass vial, which is closed with a Teflon faced stopper and sealed with an aluminium/polypropylene flip off seal. Each ml of solution for infusion contains 100 mg of levetiracetam.

**What Keppra looks like and contents of the pack**

Keppra concentrate for solution for infusion (Keppra concentrate) is a clear, colorless, sterile liquid. Keppra concentrate 5 ml vial is packed in a cardboard box of 10 vials.

**Marketing Authorisation Holder and Manufacturer**

Marketing Authorisation Holder: UCB Pharma S.A., Allée de la Recherche 60, B-1070 Bruxelles, Belgium.

Manufacturer: UCB Pharma SA, Chemin du Foriest, B-1420 Braine-l’Alleud, Belgium or UCB Pharma S.p.A., Via Praglia, 15, I-10044 Pianezza, Italy.

**Local representatives**

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

<table>
<thead>
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<th>België/Belgique/Belgien</th>
<th>Luxembourg/Luxemburg</th>
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<tr>
<td>UCB Pharma SA /NV</td>
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<tr>
<td>Ю СИ БИ Търговско представителство</td>
<td>UCB Magyarország Kft.</td>
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<tr>
<td>Тел.: + 359 (0) 2 962 99 20</td>
<td>Тел.: + 36-(1) 391 0060</td>
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<tr>
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<tr>
<td>UCB s.r.o.</td>
<td>Pharmsud Ltd.</td>
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<td>Tel: + 42 - (0) 221 773 411</td>
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This leaflet was last approved on {date}

Detailed information on this medicine is available on the European Medicines Agency (EMEA) website: http://www.emea.europa.eu

The following information is intended for medical or healthcare professionals only:
Direction for the proper use of Keppra is provided in section 3.

One vial of Keppra concentrate contains 500 mg levetiracetam (5 ml concentrate of 100 mg/ml). See Table 1 for the recommended preparation and administration of Keppra concentrate to achieve a total daily dose of 500 mg, 1000 mg, 2000 mg, or 3000 mg in two divided doses.
Table 1. Preparation and administration of Keppra concentrate

<table>
<thead>
<tr>
<th>Dose</th>
<th>Withdrawal Volume</th>
<th>Volume of Diluent</th>
<th>Infusion Time</th>
<th>Frequency of administration</th>
<th>Total Daily Dose</th>
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<tbody>
<tr>
<td>250 mg</td>
<td>2.5 ml (half 5 ml vial)</td>
<td>100 ml</td>
<td>15 minutes</td>
<td>Twice daily</td>
<td>500 mg/day</td>
</tr>
<tr>
<td>500 mg</td>
<td>5 ml (one 5 ml vial)</td>
<td>100 ml</td>
<td>15 minutes</td>
<td>Twice daily</td>
<td>1000 mg/day</td>
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<tr>
<td>1000 mg</td>
<td>10 ml (two 5 ml vials)</td>
<td>100 ml</td>
<td>15 minutes</td>
<td>Twice daily</td>
<td>2000 mg/day</td>
</tr>
<tr>
<td>1500 mg</td>
<td>15 ml (three 5 ml vials)</td>
<td>100 ml</td>
<td>15 minutes</td>
<td>Twice daily</td>
<td>3000 mg/day</td>
</tr>
</tbody>
</table>

This medicinal product is for single use only, any unused solution should be discarded.

In use shelf life: from a microbiological point of view, the product should be used immediately after dilution. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Keppra concentrate was found to be physically compatible and chemically stable when mixed with the following diluents for at least 24 hours and stored in PVC bags at controlled room temperature 15-25°C.

Diluents:
- Sodium chloride (0.9%) injection
- Lactated Ringer’s injection
- Dextrose 5% injection