

**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 the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.

Blue, 13mm oblong, scored and debossed with the code “ucb” and “250” on one side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

## 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 adults and adolescents 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, adolescents, children and infants from 1 month 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

#### Posology

##### *Monotherapy for 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 for adults ( $\geq 18$ 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.

#### Discontinuation

If levetiracetam has to be discontinued it is recommended to withdraw it gradually (*e.g.* in adults and adolescents weighing more than 50 kg: 500 mg decreases twice daily every two to four weeks; in

infants older than 6 months, children and adolescents weighting less than 50 kg: dose decrease should not exceed 10 mg/kg twice daily every two weeks; in infants (less than 6 months): dose decrease should not exceed 7 mg/kg twice daily every two weeks).

### Special populations

#### *Elderly (65 years and older)*

Adjustment of the dose is recommended in elderly patients with compromised renal function (see “Renal impairment” below).

#### *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, for adults and adolescents weighting 50 kg or more, the following formula:

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

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

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

Dosing adjustment for adult and adolescents patients weighing more than 50 kg with impaired renal function:

Group	Creatinine clearance (ml/min/1.73m <sup>2</sup> )	Dose and frequency
Normal	> 80	500 to 1,500 mg twice daily
Mild	50-79	500 to 1,000 mg twice daily
Moderate	30-49	250 to 750 mg twice daily
Severe	< 30	250 to 500 mg twice daily
End-stage renal disease patients undergoing dialysis <sup>(1)</sup>	-	500 to 1,000 mg once daily <sup>(2)</sup>

<sup>(1)</sup> A 750 mg loading dose is recommended on the first day of treatment with levetiracetam.

<sup>(2)</sup> 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.

The CLcr in ml/min/1.73 m<sup>2</sup> may be estimated from serum creatinine (mg/dl) determination, for young adolescents, children and infants, using the following formula (Schwartz formula):

$$\text{CLcr (ml/min/1.73 m}^2\text{)} = \frac{\text{Height (cm)} \times \text{ks}}{\text{Serum Creatinine (mg/dl)}}$$

ks= 0.45 in Term infants to 1 year old; ks= 0.55 in Children to less than 13 years and in adolescent female; ks= 0.7 in adolescent male

Dosing adjustment for infants, children and adolescents patients weighing less than 50 kg with impaired renal function:

Group	Creatinine clearance (ml/min/1.73 m <sup>2</sup> )	Dose and frequency <sup>(1)</sup>	
		Infants 1 to less than 6 months	Infants 6 to 23 months, children and adolescents weighing less than 50 kg
Normal	> 80	7 to 21 mg/kg (0.07 to 0.21 ml/kg) twice daily	10 to 30 mg/kg (0.10 to 0.30 ml/kg) twice daily
Mild	50-79	7 to 14 mg/kg (0.07 to 0.14 ml/kg) twice daily	10 to 20 mg/kg (0.10 to 0.20 ml/kg) twice daily
Moderate	30-49	3.5 to 10.5 mg/kg (0.035 to 0.105 ml/kg) twice daily	5 to 15 mg/kg (0.05 to 0.15 ml/kg) twice daily
Severe	< 30	3.5 to 7 mg/kg (0.035 to 0.07 ml/kg) twice daily	5 to 10 mg/kg (0.05 to 0.10 ml/kg) twice daily
End-stage renal disease patients undergoing dialysis	--	7 to 14 mg/kg (0.07 to 0.14 ml/kg) once daily <sup>(2) (4)</sup>	10 to 20 mg/kg (0.10 to 0.20 ml/kg) once daily <sup>(3) (5)</sup>

<sup>(1)</sup> Keppra oral solution should be used for doses under 250 mg, for doses not multiple of 250 mg when dosing recommendation is not achievable by taking multiple tablets and for patients unable to swallow tablets.

<sup>(2)</sup> A 10.5 mg/kg (0.105 ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.

<sup>(3)</sup> A 15 mg/kg (0.15 ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.

<sup>(4)</sup> Following dialysis, a 3.5 to 7 mg/kg (0.035 to 0.07 ml/kg) supplemental dose is recommended.

<sup>(5)</sup> Following dialysis, a 5 to 10 mg/kg (0.05 to 0.10 ml/kg) supplemental dose is recommended.

### *Hepatic impairment*

No dose adjustment is needed in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the creatinine clearance may underestimate the renal insufficiency. Therefore a 50 % reduction of the daily maintenance dose is recommended when the creatinine clearance is < 60 ml/min/1.73 m<sup>2</sup>.

### Paediatric population

The physician should prescribe the most appropriate pharmaceutical form, presentation and strength according to age, weight and dose.

The tablet formulation is not adapted for use in infants and children under the age of 6 years. Keppra oral solution is the preferred formulation for use in this population. In addition, the available dose strengths of the tablets are not appropriate for initial treatment in children weighing less than 25 kg, for patients unable to swallow tablets or for the administration of doses below 250 mg. In all of the above cases Keppra oral solution should be used.

### *Monotherapy*

The safety and efficacy of Keppra in children and adolescents below 16 years as monotherapy treatment have not been established.

No data are available.

*Add-on therapy for infants aged from 6 to 23 months, children (2 to 11 years) and adolescents (12 to 17 years) weighing less than 50 kg*

Keppra oral solution is the preferred formulation for use in infants and children under the age of 6 years.

For children 6 years and above, Keppra oral solution should be used for doses under 250 mg, for doses not multiple of 250 mg when dosing recommendation is not achievable by taking multiple tablets and for patients unable to swallow tablets

The lowest effective dose should be used. The starting dose for a child or adolescent of 25kg should be 250mg twice daily with a maximum dose of 750mg twice daily.

Dose in children 50 kg or greater is the same as in adults.

*Add-on therapy for infants aged from 1 month to less than 6 months*

The oral solution is the formulation to use in infants.

#### 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.

### **4.3 Contraindications**

Hypersensitivity to the active substance or other pyrrolidone derivatives or to any of the excipients listed in section 6.1.

### **4.4 Special warnings and precautions for use**

#### Renal impairment

The administration of levetiracetam to patients with renal impairment may require dose adjustment. In patients with severely impaired hepatic function, assessment of renal function is recommended before dose selection (see section 4.2).

#### Acute Kidney injury

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

#### Blood cell counts

Rare cases of decreased blood cell counts (neutropenia, agranulocytosis, leucopenia, thrombocytopenia and pancytopenia) have been described in association with levetiracetam administration, generally at the beginning of the treatment. Complete blood cell counts are advised in patients experiencing important weakness, pyrexia, recurrent infections or coagulation disorders (section 4.8).

#### Suicide

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

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

#### Paediatric population

The tablet formulation is not adapted for use in infants and children under the age of 6 years.

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.

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

##### Antiepileptic medicinal products

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

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 20 % higher levetiracetam clearance in children taking enzyme-inducing antiepileptic medicinal products. Dose adjustment is not required.

##### Probenecid

Probenecid (500 mg four times daily), a renal tubular secretion blocking agent, has been shown to inhibit the renal clearance of the primary metabolite, but not of levetiracetam. Nevertheless, the concentration of this metabolite remains low.

##### Methotrexate

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

##### Oral contraceptives and other pharmacokinetics interactions

Levetiracetam 1,000 mg daily did not influence the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel); endocrine parameters (luteinizing hormone and progesterone) were not modified. -Levetiracetam 2,000 mg daily did not influence the pharmacokinetics of digoxin and warfarin; prothrombin times were not modified. Co-administration with digoxin, oral contraceptives and warfarin did not influence the pharmacokinetics of levetiracetam.

##### Laxatives

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

##### Food and alcohol

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

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

#### **4.6 Fertility, pregnancy and lactation**

##### Pregnancy

Postmarketing data from several prospective pregnancy registries have documented outcomes in over 1,000 women exposed to levetiracetam monotherapy during the first trimester of pregnancy. Overall, these data do not suggest a substantial increase in the risk for major congenital malformations,

although a teratogenic risk cannot be completely excluded. Therapy with multiple antiepileptic medicinal products is associated with a higher risk of congenital malformations than monotherapy and, therefore, monotherapy should be considered. Studies in animals have shown reproductive toxicity (see section 5.3).

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

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.

#### Breastfeeding

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.

#### Fertility

No impact on fertility was detected in animal studies (see section 5.3). No clinical data are available, potential risk for human is unknown.

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

Levetiracetam has minor or moderate influence on the ability to drive and use machines. Due to possible different individual sensitivity, some patients might experience somnolence or other central nervous system related symptoms, especially at the beginning of treatment or following a dose increase. Therefore, caution is recommended in those patients when performing skilled tasks, *e.g.* driving vehicles or operating machinery. Patients are advised not to drive or use machines until it is established that their ability to perform such activities is not affected.

### **4.8 Undesirable effects**

#### Summary of the safety profile

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

#### Tabulated list of adverse reactions

Adverse reactions reported in clinical studies (adults, adolescents, children and infants > 1 month) and from post-marketing experience are listed in the following table per System Organ Class and per frequency. Adverse reactions are presented in the order of decreasing seriousness and their frequency is defined as follows: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ) and very rare ( $< 1/10,000$ ).

<u>MedDRA SOC</u>	<u>Frequency category</u>			
	<u>Very common</u>	<u>Common</u>	<u>Uncommon</u>	<u>Rare</u>
<u>Infections and infestations</u>	Nasopharyngitis			Infection
<u>Blood and lymphatic system disorders</u>			Thrombocytopenia, leukopenia	Pancytopenia, neutropenia, agranulocytosis
<u>Immune system disorders</u>				Drug reaction with eosinophilia and systemic symptoms (DRESS), Hypersensitivity (including angioedema and anaphylaxis)
<u>Metabolism and nutrition disorders</u>		Anorexia	Weight decreased, weight increase	Hyponatraemia
<u>Psychiatric disorders</u>		Depression, hostility/aggression, anxiety, insomnia, nervousness/irritability	Suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusional state, panic attack, affect lability/mood swings, agitation	Completed suicide, personality disorder, thinking abnormal
<u>Nervous system disorders</u>	Somnolence, headache	Convulsion, balance disorder, dizziness, lethargy, tremor	Amnesia, memory impairment, coordination abnormal/ataxia, paraesthesia, disturbance in attention	Choreoathetosis, dyskinesia, hyperkinesia
<u>Eye disorders</u>			Diplopia, vision blurred	
<u>Ear and labyrinth disorders</u>		Vertigo		
<u>Respiratory, thoracic and mediastinal disorders</u>		Cough		
<u>Gastrointestinal disorders</u>		Abdominal pain, diarrhoea, dyspepsia, vomiting, nausea		Pancreatitis
<u>Hepatobiliary disorders</u>			Liver function test abnormal	Hepatic failure, hepatitis
<u>Renal and Urinary Disorders</u>				Acute Kidney injury
<u>Skin and subcutaneous tissue disorders</u>		Rash	Alopecia, eczema, pruritus,	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme



<u>MedDRA SOC</u>	<u>Frequency category</u>			
	<u>Very common</u>	<u>Common</u>	<u>Uncommon</u>	<u>Rare</u>
<u>Musculoskeletal and connective tissue disorders</u>			Muscular weakness, myalgia	Rhabdomyolysis and blood creatine phosphokinase increased*
<u>General disorders and administration site conditions</u>		Asthenia/fatigue		
<u>Injury, poisoning and procedural complications</u>			Injury	

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

Cases of encephalopathy have been rarely observed after levetiracetam administration. These undesirable effects generally occurred at the beginning of the treatment (few days to a few months) and were reversible after treatment discontinuation.

#### Description of selected adverse reactions

The risk of anorexia is higher when levetiracetam is coadministered with topiramate. In several cases of alopecia, recovery was observed when levetiracetam was discontinued. Bone marrow suppression was identified in some of the cases of pancytopenia.

#### Paediatric population

In patients aged 1 month to less than 4 years, a total of 190 patients have been treated with levetiracetam in placebo-controlled and open label extension studies. Sixty of these patients were treated with levetiracetam in placebo-controlled studies. In patients aged 4-16 years, a total of 645 patients have been treated with levetiracetam in placebo-controlled and open label extension studies. 233 of these patients were treated with levetiracetam in placebo-controlled studies. In both these paediatric age ranges, these data are supplemented with the post-marketing experience of the use of levetiracetam.

In addition, 101 infants aged less than 12 months have been exposed in a post authorization safety study. No new safety concerns for levetiracetam were identified for infants less than 12 months of age with epilepsy.

The adverse reaction profile of levetiracetam is generally similar across age groups and across the approved epilepsy indications. Safety results in paediatric patients in placebo-controlled clinical studies were consistent with the safety profile of levetiracetam in adults except for behavioural and psychiatric adverse reactions which were more common in children than in adults. In children and adolescents aged 4 to 16 years, vomiting (very common, 11.2%), agitation (common, 3.4%), mood swings (common, 2.1%), affect lability (common, 1.7%), aggression (common, 8.2%), abnormal behaviour (common, 5.6%), and lethargy (common, 3.9%) were reported more frequently than in other age ranges or in the overall safety profile. In infants and children aged 1 month to less than 4 years, irritability (very common, 11.7%) and coordination abnormal (common, 3.3%) were reported more frequently than in other age groups or in the overall safety profile.

A double-blind, placebo-controlled paediatric safety study with a non-inferiority design has assessed the cognitive and neuropsychological effects of levetiracetam in children 4 to 16 years of age with partial onset seizures. It was concluded that Keppra was not different (non inferior) from placebo with regard to the change from baseline of the Leiter-R Attention and Memory, Memory Screen Composite

score in the per-protocol population. Results related to behavioural and emotional functioning indicated a worsening in levetiracetam treated patients on aggressive behaviour as measured in a standardised and systematic way using a validated instrument (CBCL – Achenbach Child Behavior Checklist). However subjects, who took levetiracetam in the long-term open label follow-up study, did not experience a worsening, on average, in their behavioural and emotional functioning; in particular measures of aggressive behaviour were not worse than baseline.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## **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, other antiepileptics, ATC code: N03AX14.

The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of  $\alpha$ -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. *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  $\beta$ -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 efficacy and safety

*Adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents, children and infants from 1 month 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.

### Paediatric population

In paediatric 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.

In paediatric patients (1 month to less than 4 years of age), levetiracetam efficacy was established in a double-blind, placebo-controlled study, which included 116 patients and had a treatment duration of 5 days. In this study, patients were prescribed 20 mg/kg, 25 mg/kg, 40 mg/kg or 50 mg/kg daily dose of oral solution based on their age titration schedule. A dose of 20 mg/kg/day titrating to 40 mg/kg/day for infants one month to less than six months and a dose of 25 mg/kg/day titrating to 50 mg/kg/day for infants and children 6 months to less than 4 years old, was use in this study. The total daily dose was administered twice daily.

The primary measure of effectiveness was the responder rate (percent of patients with  $\geq 50$  % reduction from baseline in average daily partial onset seizure frequency) assessed by a blinded central reader using a 48-hour video EEG. The efficacy analysis consisted of 109 patients who had at least 24 hours of video EEG in both baseline and evaluation periods. 43.6 % of the levetiracetam treated patients and 19.6 % of the patients on placebo were considered as responders. The results are consistent across age group. With continued long-term treatment, 8.6 % of the patients were seizure-free for at least 6 months and 7.8 % were seizure-free for at least 1 year.

35 infants aged less than 1 year with partial onset seizures have been exposed in placebo-control clinical studies of which only 13 were aged < 6 months.

*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<sub>450</sub> 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<sub>450</sub> 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).

#### 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).

#### Paediatric population

##### *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).

In the population pharmacokinetic analysis conducted in patients from 1 month to 16 years of age, body weight was significantly correlated to apparent clearance (clearance increased with an increase in body weight) and apparent volume of distribution. Age also had an influence on both parameters. This effect was pronounced for the younger infants, and subsided as age increased, to become negligible around 4 years of age.

In both population pharmacokinetic analyses, there was about a 20 % increase of apparent clearance of levetiracetam when it was co-administered with an enzyme-inducing antiepileptic medicinal product.

### **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential.

Adverse effects not observed in clinical studies but seen in the rat and to a lesser extent in the mouse at exposure levels similar to human exposure levels and with possible relevance for clinical use were liver changes, indicating an adaptive response such as increased weight and centrilobular hypertrophy, fatty infiltration and increased liver enzymes in plasma.

No adverse reactions on male or female fertility or reproduction performance were observed in rats at doses up to 1800 mg/kg/day (x 6 the MRHD on a mg/m<sup>2</sup> or exposure basis) in parents and F1 generation.

Two embryo-foetal development (EFD) studies were performed in rats at 400, 1200 and 3600 mg/kg/day. At 3600 mg/kg/day, in only one of the 2 EFD studies, there was a slight decrease in foetal weight associated with a marginal increase in skeletal variations/minor anomalies. There was no effect on embryomortality and no increased incidence of malformations. The NOAEL (No Observed Adverse Effect Level) was 3600 mg/kg/day for pregnant female rats (x 12 the MRHD on a mg/m<sup>2</sup> basis) and 1200 mg/kg/day for fetuses.

Four embryo-foetal development studies were performed in rabbits covering doses of 200, 600, 800, 1200 and 1800 mg/kg/day. The dose level of 1800 mg/kg/day induced a marked maternal toxicity and a decrease in foetal weight associated with increased incidence of foetuses with cardiovascular/skeletal anomalies. The NOAEL was <200 mg/kg/day for the dams and 200 mg/kg/day for the fetuses (equal to the MRHD on a mg/m<sup>2</sup> basis).

A peri- and post-natal development study was performed in rats with levetiracetam doses of 70, 350 and 1800 mg/kg/day. The NOAEL was ≥ 1800 mg/kg/day for the F0 females, and for the survival, growth and development of the F1 offspring up to weaning (x 6 the MRHD on a mg/m<sup>2</sup> basis).

Neonatal and juvenile animal studies in rats and dogs demonstrated that there were no adverse effects seen in any of the standard developmental or maturation endpoints at doses up to 1800 mg/kg/day (x 6 – 17 the MRHD on a mg/m<sup>2</sup> basis).

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Tablet core

Croscarmellose sodium  
Macrogol 6000  
Silica colloidal anhydrous  
Magnesium stearate

#### Film-coating

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**

This medicinal product does not require any special storage conditions.

#### **6.5 Nature and contents of container**

Aluminium/PVC blisters placed into cardboard boxes containing 20, 30, 50, 60, 100 film-coated tablets and multipacks containing 200 (2 packs of 100) film-coated tablets.

Aluminium/PVC perforated unit dose blisters placed into cardboard boxes containing 100 x 1 film-coated tablet.

Not all pack sizes may be marketed.

#### **6.6 Special precautions for disposal**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

### **7. MARKETING AUTHORISATION HOLDER**

UCB Pharma SA  
Allée de la Recherche 60  
B-1070 Brussels  
Belgium

### **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  
EU/1/00/146/034

### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 29 September 2000  
Date of latest renewal: 20 August 2015

### **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>



## 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 the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.

Yellow, 16 mm oblong, scored and debossed with the code “ucb” and “500” on one side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

## 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 adults and adolescents 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, adolescents, children and infants from 1 month 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

#### Posology

##### *Monotherapy for 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 for adults ( $\geq 18$ 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.

#### Discontinuation

If levetiracetam has to be discontinued it is recommended to withdraw it gradually (*e.g.* in adults and adolescents weighing more than 50 kg: 500 mg decreases twice daily every two to four weeks; in infants older than 6 months, children and adolescents weighing less than 50 kg: dose decrease should not exceed 10 mg/kg twice daily every two weeks; in infants (less than 6 months): dose decrease should not exceed 7 mg/kg twice daily every two weeks).

### Special populations

#### *Elderly (65 years and older)*

Adjustment of the dose is recommended in elderly patients with compromised renal function (see “Renal impairment” below).

#### *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, for adults and adolescents weighing 50 kg or more, the following formula:

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

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

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

Dosing adjustment for adult and adolescents patients weighing more than 50 kg with impaired renal function:

Group	Creatinine clearance (ml/min/1.73m <sup>2</sup> )	Dose and frequency
Normal	> 80	500 to 1,500 mg twice daily
Mild	50-79	500 to 1,000 mg twice daily
Moderate	30-49	250 to 750 mg twice daily
Severe	< 30	250 to 500 mg twice daily
End-stage renal disease patients undergoing dialysis <sup>(1)</sup>	-	500 to 1,000 mg once daily <sup>(2)</sup>

<sup>(1)</sup> A 750 mg loading dose is recommended on the first day of treatment with levetiracetam.

<sup>(2)</sup> 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.

The CLCr in ml/min/1.73 m<sup>2</sup> may be estimated from serum creatinine (mg/dl) determination, for young adolescents, children and infants, using the following formula (Schwartz formula):

$$\text{CLCr (ml/min/1.73 m}^2\text{)} = \frac{\text{Height (cm)} \times \text{ks}}{\text{Serum Creatinine (mg/dl)}}$$

ks= 0.45 in Term infants to 1 year old; ks= 0.55 in Children to less than 13 years and in adolescent female; ks= 0.7 in adolescent male

Dosing adjustment for infants, children and adolescents patients weighing less than 50 kg with impaired renal function:

Group	Creatinine clearance (ml/min/1.73m <sup>2</sup> )	Dose and frequency <sup>(1)</sup>	
		Infants 1 to less than 6 months	Infants 6 to 23 months, children and adolescents weighing less than 50 kg
Normal	> 80	7 to 21 mg/kg (0.07 to 0.21 ml/kg) twice daily	10 to 30 mg/kg (0.10 to 0.30 ml/kg) twice daily
Mild	50-79	7 to 14 mg/kg (0.07 to 0.14 ml/kg) twice daily	10 to 20 mg/kg (0.10 to 0.20 ml/kg) twice daily
Moderate	30-49	3.5 to 10.5 mg/kg (0.035 to 0.105 ml/kg) twice daily	5 to 15 mg/kg (0.05 to 0.15 ml/kg) twice daily
Severe	< 30	3.5 to 7 mg/kg (0.035 to 0.07 ml/kg) twice daily	5 to 10 mg/kg (0.05 to 0.10 ml/kg) twice daily
End-stage renal disease patients undergoing dialysis	--	7 to 14 mg/kg (0.07 to 0.14 ml/kg) once daily <sup>(2)</sup> <sup>(4)</sup>	10 to 20 mg/kg (0.10 to 0.20 ml/kg) once daily <sup>(3)</sup> <sup>(5)</sup>

<sup>(1)</sup> Keppra oral solution should be used for doses under 250 mg, for doses not multiple of 250 mg when dosing recommendation is not achievable by taking multiple tablets and for patients unable to swallow tablets.

<sup>(2)</sup> A 10.5 mg/kg (0.105 ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.

<sup>(3)</sup> A 15 mg/kg (0.15 ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.

<sup>(4)</sup> Following dialysis, a 3.5 to 7 mg/kg (0.035 to 0.07 ml/kg) supplemental dose is recommended.

<sup>(5)</sup> Following dialysis, a 5 to 10 mg/kg (0.05 to 0.10 ml/kg) supplemental dose is recommended.

### *Hepatic impairment*

No dose adjustment is needed in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the creatinine clearance may underestimate the renal insufficiency. Therefore a 50 % reduction of the daily maintenance dose is recommended when the creatinine clearance is < 60 ml/min/1.73 m<sup>2</sup>.

### Paediatric population

The physician should prescribe the most appropriate pharmaceutical form, presentation and strength according to age, weight and dose.

The tablet formulation is not adapted for use in infants and children under the age of 6 years. Keppra oral solution is the preferred formulation for use in this population. In addition, the available dose strengths of the tablets are not appropriate for initial treatment in children weighing less than 25 kg, for patients unable to swallow tablets or for the administration of doses below 250 mg. In all of the above cases Keppra oral solution should be used.

### *Monotherapy*

The safety and efficacy of Keppra in children and adolescents below 16 years as monotherapy treatment have not been established.

No data are available.

*Add-on therapy for infants aged 6 to 23 months, children (2 to 11 years) and adolescents (12 to 17 years) weighing less than 50 kg*

Keppra oral solution is the preferred formulation for use in infants and children under the age of 6 years.

For children 6 years and above, Keppra oral solution should be used for doses under 250 mg, for doses not multiple of 250 mg when dosing recommendation is not achievable by taking multiple tablets and for patients unable to swallow tablets.

The lowest effective dose should be used. The starting dose for a child or adolescent of 25kg should be 250mg twice daily with a maximum dose of 750mg twice daily. Dose in children 50 kg or greater is the same as in adults.

*Add-on therapy for infants aged from 1 month to less than 6 months*

The oral solution is the formulation to use in infants.

#### 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.

### **4.3 Contraindications**

Hypersensitivity to the active substance or other pyrrolidone derivatives or to any of the excipients listed in section 6.1.

### **4.4 Special warnings and precautions for use**

#### Renal impairment

The administration of levetiracetam to patients with renal impairment may require dose adjustment. In patients with severely impaired hepatic function, assessment of renal function is recommended before dose selection (see section 4.2).

#### Acute Kidney injury

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

#### Blood cell counts

Rare cases of decreased blood cell counts (neutropenia, agranulocytosis, leucopenia, thrombocytopenia and pancytopenia) have been described in association with levetiracetam administration, generally at the beginning of the treatment. Complete blood cell counts are advised in patients experiencing important weakness, pyrexia, recurrent infections or coagulation disorders (section 4.8).

#### Suicide

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

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

### Paediatric population

The tablet formulation is not adapted for use in infants and children under the age of 6 years.

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.

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

### Antiepileptic medicinal products

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

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 20 % higher levetiracetam clearance in children taking enzyme-inducing antiepileptic medicinal products. Dose adjustment is not required.

### Probenecid

Probenecid (500 mg four times daily), a renal tubular secretion blocking agent, has been shown to inhibit the renal clearance of the primary metabolite, but not of levetiracetam. Nevertheless, the concentration of this metabolite remains low.

### Methotrexate

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

### Oral contraceptives and other pharmacokinetics interactions

Levetiracetam 1,000 mg daily did not influence the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel); endocrine parameters (luteinizing hormone and progesterone) were not modified. Levetiracetam 2,000 mg daily did not influence the pharmacokinetics of digoxin and warfarin; prothrombin times were not modified. Co-administration with digoxin, oral contraceptives and warfarin did not influence the pharmacokinetics of levetiracetam.

### Laxatives

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

### Food and alcohol

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

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

## **4.6 Fertility, pregnancy and lactation**

### Pregnancy

Postmarketing data from several prospective pregnancy registries have documented outcomes in over 1,000 women exposed to levetiracetam monotherapy during the first trimester of pregnancy. Overall,

these data do not suggest a substantial increase in the risk for major congenital malformations, although a teratogenic risk cannot be completely excluded. Therapy with multiple antiepileptic medicinal products is associated with a higher risk of congenital malformations than monotherapy and, therefore, monotherapy should be considered. Studies in animals have shown reproductive toxicity (see section 5.3).

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

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.

#### Breastfeeding

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.

#### Fertility

No impact on fertility was detected in animal studies (see section 5.3). No clinical data are available, potential risk for human is unknown.

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

Levetiracetam has minor or moderate influence on the ability to drive and use machines. Due to possible different individual sensitivity, some patients might experience somnolence or other central nervous system related symptoms, especially at the beginning of treatment or following a dose increase. Therefore, caution is recommended in those patients when performing skilled tasks, *e.g.* driving vehicles or operating machinery. Patients are advised not to drive or use machines until it is established that their ability to perform such activities is not affected.

### **4.8 Undesirable effects**

#### Summary of the safety profile

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

#### Tabulated list of adverse reactions

Adverse reactions reported in clinical studies (adults, adolescents, children and infants > 1 month) and from post-marketing experience are listed in the following table per System Organ Class and per frequency. Adverse reactions are presented in the order of decreasing seriousness and their frequency is defined as follows: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ) and very rare ( $< 1/10,000$ ).

<u>MedDRA SOC</u>	<u>Frequency category</u>			
	<u>Very common</u>	<u>Common</u>	<u>Uncommon</u>	<u>Rare</u>
<u>Infections and infestations</u>	Nasopharyngitis			Infection
<u>Blood and lymphatic system disorders</u>			Thrombocytopenia, leukopenia	Pancytopenia, neutropenia, agranulocytosis
<u>Immune system disorders</u>				Drug reaction with eosinophilia and systemic symptoms (DRESS), Hypersensitivity (including angioedema and anaphylaxis)
<u>Metabolism and nutrition disorders</u>		Anorexia	Weight decreased, weight increase	Hyponatraemia
<u>Psychiatric disorders</u>		Depression, hostility/aggression, anxiety, insomnia, nervousness/irritability	Suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusional state, panic attack, affect lability/mood swings, agitation	Completed suicide, personality disorder, thinking abnormal
<u>Nervous system disorders</u>	Somnolence, headache	Convulsion, balance disorder, dizziness, lethargy, tremor	Amnesia, memory impairment, coordination abnormal/ataxia, paraesthesia, disturbance in attention	Choreoathetosis, dyskinesia, hyperkinesia
<u>Eye disorders</u>			Diplopia, vision blurred	
<u>Ear and labyrinth disorders</u>		Vertigo		
<u>Respiratory, thoracic and mediastinal disorders</u>		Cough		
<u>Gastrointestinal disorders</u>		Abdominal pain, diarrhoea, dyspepsia, vomiting, nausea		Pancreatitis
<u>Hepatobiliary disorders</u>			Liver function test abnormal	Hepatic failure, hepatitis
<u>Renal and Urinary Disorders</u>				Acute Kidney injury
<u>Skin and subcutaneous tissue disorders</u>		Rash	Alopecia, eczema, pruritus,	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme

<u>MedDRA SOC</u>	<u>Frequency category</u>			
	<u>Very common</u>	<u>Common</u>	<u>Uncommon</u>	<u>Rare</u>
<u>Musculoskeletal and connective tissue disorders</u>			Muscular weakness, myalgia	Rhabdomyolysis and blood creatine phosphokinase increased*
<u>General disorders and administration site conditions</u>		Asthenia/fatigue		
<u>Injury, poisoning and procedural complications</u>			Injury	

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

Cases of encephalopathy have been rarely observed after levetiracetam administration. These undesirable effects generally occurred at the beginning of the treatment (few days to a few months) and were reversible after treatment discontinuation.

#### Description of selected adverse reactions

The risk of anorexia is higher when levetiracetam is coadministered with topiramate. In several cases of alopecia, recovery was observed when levetiracetam was discontinued. Bone marrow suppression was identified in some of the cases of pancytopenia.

#### Paediatric population

In patients aged 1 month to less than 4 years, a total of 190 patients have been treated with levetiracetam in placebo-controlled and open label extension studies. Sixty of these patients were treated with levetiracetam in placebo-controlled studies. In patients aged 4-16 years, a total of 645 patients have been treated with levetiracetam in placebo-controlled and open label extension studies. 233 of these patients were treated with levetiracetam in placebo-controlled studies. In both these paediatric age ranges, these data are supplemented with the post-marketing experience of the use of levetiracetam.

In addition, 101 infants aged less than 12 months have been exposed in a post authorization safety study. No new safety concerns for levetiracetam were identified for infants less than 12 months of age with epilepsy.

The adverse reaction profile of levetiracetam is generally similar across age groups and across the approved epilepsy indications. Safety results in paediatric patients in placebo-controlled clinical studies were consistent with the safety profile of levetiracetam in adults except for behavioural and psychiatric adverse reactions which were more common in children than in adults. In children and adolescents aged 4 to 16 years, vomiting (very common, 11.2%), agitation (common, 3.4%), mood swings (common, 2.1%), affect lability (common, 1.7%), aggression (common, 8.2%), abnormal behaviour (common, 5.6%), and lethargy (common, 3.9%) were reported more frequently than in other age ranges or in the overall safety profile. In infants and children aged 1 month to less than 4 years, irritability (very common, 11.7%) and coordination abnormal (common, 3.3%) were reported more frequently than in other age groups or in the overall safety profile.

A double-blind, placebo-controlled paediatric safety study with a non-inferiority design has assessed the cognitive and neuropsychological effects of levetiracetam in children 4 to 16 years of age with partial onset seizures. It was concluded that Keppra was not different (non inferior) from placebo with regard to the change from baseline of the Leiter-R Attention and Memory, Memory Screen Composite



score in the per-protocol population. Results related to behavioural and emotional functioning indicated a worsening in levetiracetam-treated patients on aggressive behaviour as measured in a standardised and systematic way using a validated instrument (CBCL – Achenbach Child Behavior Checklist). However subjects, who took levetiracetam in the long-term open label follow-up study, did not experience a worsening, on average, in their behavioural and emotional functioning; in particular measures of aggressive behaviour were not worse than baseline.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## **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, other antiepileptics, ATC code: N03AX14.  
The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of  $\alpha$ -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. *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  $\beta$ -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 efficacy and safety

*Adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents, children and infants from 1 month 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.

### Paediatric population

In paediatric 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.

In paediatric patients (1 month to less than 4 years of age), levetiracetam efficacy was established in a double-blind, placebo-controlled study, which included 116 patients and had a treatment duration of 5 days. In this study, patients were prescribed 20 mg/kg, 25 mg/kg, 40 mg/kg or 50 mg/kg daily dose of oral solution based on their age titration schedule. A dose of 20 mg/kg/day titrating to 40 mg/kg/day for infants one month to less than six months and a dose of 25 mg/kg/day titrating to 50 mg/kg/day for infants and children 6 months to less than 4 years old, was used in this study. The total daily dose was administered twice daily.

The primary measure of effectiveness was the responder rate (percent of patients with  $\geq 50$  % reduction from baseline in average daily partial onset seizure frequency) assessed by a blinded central reader using a 48-hour video EEG. The efficacy analysis consisted of 109 patients who had at least 24 hours of video EEG in both baseline and evaluation periods. 43.6 % of the levetiracetam treated patients and 19.6 % of the patients on placebo were considered as responders. The results are consistent across age group. With continued long-term treatment, 8.6 % of the patients were seizure-free for at least 6 months and 7.8 % were seizure-free for at least 1 year.

35 infants aged less than 1 year with partial onset seizures have been exposed in placebo-control clinical studies of which only 13 were aged < 6 months.

*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  $\mu\text{g/ml}$  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<sub>450</sub> 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<sub>450</sub> 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  $7 \pm 1$  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).

#### 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).

#### Paediatric population

##### *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).

In the population pharmacokinetic analysis conducted in patients from 1 month to 16 years of age, body weight was significantly correlated to apparent clearance (clearance increased with an increase in body weight) and apparent volume of distribution. Age also had an influence on both parameters. This effect was pronounced for the younger infants, and subsided as age increased, to become negligible around 4 years of age.

In both population pharmacokinetic analyses, there was about a 20 % increase of apparent clearance of levetiracetam when it was co-administered with an enzyme-inducing antiepileptic medicinal product.

### **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential.

Adverse effects not observed in clinical studies but seen in the rat and to a lesser extent in the mouse at exposure levels similar to human exposure levels and with possible relevance for clinical use were liver changes, indicating an adaptive response such as increased weight and centrilobular hypertrophy, fatty infiltration and increased liver enzymes in plasma.

No adverse reactions on male or female fertility or reproduction performance were observed in rats at doses up to 1800 mg/kg/day (x 6 the MRHD on a mg/m<sup>2</sup> or exposure basis) in parents and F1 generation.

Two embryo-foetal development (EFD) studies were performed in rats at 400, 1200 and 3600 mg/kg/day. At 3600 mg/kg/day, in only one of the 2 EFD studies, there was a slight decrease in foetal weight associated with a marginal increase in skeletal variations/minor anomalies. There was no effect on embryomortality and no increased incidence of malformations. The NOAEL (No Observed Adverse Effect Level) was 3600 mg/kg/day for pregnant female rats (x 12 the MRHD on a mg/m<sup>2</sup> basis) and 1200 mg/kg/day for fetuses.

Four embryo-foetal development studies were performed in rabbits covering doses of 200, 600, 800, 1200 and 1800 mg/kg/day. The dose level of 1800 mg/kg/day induced a marked maternal toxicity and a decrease in foetal weight associated with increased incidence of fetuses with cardiovascular/skeletal anomalies. The NOAEL was <200 mg/kg/day for the dams and 200 mg/kg/day for the fetuses (equal to the MRHD on a mg/m<sup>2</sup> basis).

A peri- and post-natal development study was performed in rats with levetiracetam doses of 70, 350 and 1800 mg/kg/day. The NOAEL was ≥ 1800 mg/kg/day for the F0 females, and for the survival, growth and development of the F1 offspring up to weaning (x 6 the MRHD on a mg/m<sup>2</sup> basis).

Neonatal and juvenile animal studies in rats and dogs demonstrated that there were no adverse effects seen in any of the standard developmental or maturation endpoints at doses up to 1800 mg/kg/day (x 6-17 the MRHD on a mg/m<sup>2</sup> basis)

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Tablet core:

Croscarmellose sodium

Macrogol 6000

Silica colloidal anhydrous

Magnesium stearate

Film-coating:

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**

This medicinal product does not require any special storage conditions.

#### **6.5 Nature and contents of container**

Aluminium/PVC blisters placed into cardboard boxes containing 10, 20, 30, 50, 60, 100, 120 film-coated tablets and multipacks containing 200 (2 packs of 100) film-coated tablets.

Aluminium/PVC perforated unit dose blisters placed into cardboard boxes containing 100 x 1 film-coated tablet.

Not all pack sizes may be marketed.

#### **6.6 Special precautions for disposal**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

### **7. MARKETING AUTHORISATION HOLDER**

UCB Pharma SA  
Allée de la Recherche 60  
B-1070 Brussels  
Belgium

### **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  
EU/1/00/146/035

### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 29 September 2000  
Date of latest renewal: 20 August 2015

### **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

## 1. NAME OF THE MEDICINAL PRODUCT

Kepra 750 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 750 mg levetiracetam.

### Excipient with known effect:

Each film-coated tablet contains 0.19 mg of sunset yellow FCF (E110).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.

Orange, 18 mm oblong, scored and debossed with the code “ucb” and “750” on one side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Kepra is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy.

Kepra is indicated as adjunctive therapy

- in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents, children and infants from 1 month 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

#### Posology

##### *Monotherapy for 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 for adults ( $\geq 18$ 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.



### Discontinuation

If levetiracetam has to be discontinued it is recommended to withdraw it gradually (*e.g.* in adults and adolescents weighing more than 50 kg: 500 mg decreases twice daily every two to four weeks; in infants older than 6 months, children and adolescents weighting less than 50 kg: dose decrease should not exceed 10 mg/kg twice daily every two weeks; in infants (less than 6 months): dose decrease should not exceed 7 mg/kg twice daily every two weeks).

### Special populations

#### *Elderly (65 years and older)*

Adjustment of the dose is recommended in elderly patients with compromised renal function (see “Renal impairment” below).

#### *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, for adults and adolescents weighting 50 kg or more, the following formula:

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

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

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

Dosing adjustment for adult and adolescents patients weighing more than 50 kg with impaired renal function:

Group	Creatinine clearance (ml/min/1.73m <sup>2</sup> )	Dose and frequency
Normal	> 80	500 to 1,500 mg twice daily
Mild	50-79	500 to 1,000 mg twice daily
Moderate	30-49	250 to 750 mg twice daily
Severe	< 30	250 to 500 mg twice daily
End-stage renal disease patients undergoing dialysis <sup>(1)</sup>	-	500 to 1,000 mg once daily <sup>(2)</sup>

<sup>(1)</sup> A 750 mg loading dose is recommended on the first day of treatment with levetiracetam.

<sup>(2)</sup> 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.

The CLcr in ml/min/1.73 m<sup>2</sup> may be estimated from serum creatinine (mg/dl) determination, for young adolescents, children and infants, using the following formula (Schwartz formula):

$$\text{CLcr (ml/min/1.73 m}^2\text{)} = \frac{\text{Height (cm)} \times \text{ks}}{\text{Serum Creatinine (mg/dl)}}$$

ks= 0.45 in Term infants to 1 year old; ks= 0.55 in Children to less than 13 years and in adolescent female; ks= 0.7 in adolescent male

Dosing adjustment for infants, children and adolescents patients weighing less than 50 kg with impaired renal function:

Group	Creatinine clearance (ml/min/1.73m <sup>2</sup> )	Dose and frequency <sup>(1)</sup>	
		Infants 1 to less than 6 months	Infants 6 to 23 months, children and adolescents weighing less than 50 kg
Normal	> 80	7 to 21 mg/kg (0.07 to 0.21 ml/kg) twice daily	10 to 30 mg/kg (0.10 to 0.30 ml/kg) twice daily
Mild	50-79	7 to 14 mg/kg (0.07 to 0.14 ml/kg) twice daily	10 to 20 mg/kg (0.10 to 0.20 ml/kg) twice daily
Moderate	30-49	3.5 to 10.5 mg/kg (0.035 to 0.105 ml/kg) twice daily	5 to 15 mg/kg (0.05 to 0.15 ml/kg) twice daily
Severe	< 30	3.5 to 7 mg/kg (0.035 to 0.07 ml/kg) twice daily	5 to 10 mg/kg (0.05 to 0.10 ml/kg) twice daily
End-stage renal disease patients undergoing dialysis	--	7 to 14 mg/kg (0.07 to 0.14 ml/kg) once daily <sup>(2)</sup> <sup>(4)</sup>	10 to 20 mg/kg (0.10 to 0.20 ml/kg) once daily <sup>(3)</sup> <sup>(5)</sup>

<sup>(1)</sup> Keppra oral solution should be used for doses under 250 mg, for doses not multiple of 250 mg when dosing recommendation is not achievable by taking multiple tablets and for patients unable to swallow tablets.

<sup>(2)</sup> A 10.5 mg/kg (0.105 ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.

<sup>(3)</sup> A 15 mg/kg (0.15 ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.

<sup>(4)</sup> Following dialysis, a 3.5 to 7 mg/kg (0.035 to 0.07 ml/kg) supplemental dose is recommended.

<sup>(5)</sup> Following dialysis, a 5 to 10 mg/kg (0.05 to 0.10 ml/kg) supplemental dose is recommended.

### *Hepatic impairment*

No dose adjustment is needed in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the creatinine clearance may underestimate the renal insufficiency. Therefore a 50 % reduction of the daily maintenance dose is recommended when the creatinine clearance is < 60 ml/min/1.73 m<sup>2</sup>.

### Paediatric population

The physician should prescribe the most appropriate pharmaceutical form, presentation and strength according to age, weight and dose.

The tablet formulation is not adapted for use in infants and children under the age of 6 years. Keppra oral solution is the preferred formulation for use in this population. In addition, the available dose strengths of the tablets are not appropriate for initial treatment in children weighing less than 25 kg, for patients unable to swallow tablets or for the administration of doses below 250 mg. In all of the above cases Keppra oral solution should be used.

### *Monotherapy*

The safety and efficacy of Keppra in children and adolescents below 16 years as monotherapy treatment have not been established.  
No data are available.

*Add-on therapy for infants aged 6 to 23 months, children (2 to 11 years) and adolescents (12 to 17 years) weighing less than 50 kg*

Keppra oral solution is the preferred formulation for use in infants and children under the age of 6 years.

For children 6 years and above, Keppra oral solution should be used for doses under 250 mg, for doses not multiple of 250 mg when dosing recommendation is not achievable by taking multiple tablets and for patients unable to swallow tablets

The lowest effective dose should be used. The starting dose for a child or adolescent of 25kg should be 250mg twice daily with a maximum dose of 750mg twice daily. Dose in children 50 kg or greater is the same as in adults.

*Add-on therapy for infants aged from 1 month to less than 6 months*

The oral solution is the formulation to use in infants.

#### 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.

### **4.3 Contraindications**

Hypersensitivity to the active substance or other pyrrolidone derivatives or to any of the excipients listed in section 6.1.

### **4.4 Special warnings and precautions for use**

#### Renal impairment

The administration of levetiracetam to patients with renal impairment may require dose adjustment. In patients with severely impaired hepatic function, assessment of renal function is recommended before dose selection (see section 4.2).

#### Acute Kidney injury

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

#### Blood cell counts

Rare cases of decreased blood cell counts (neutropenia, agranulocytosis, leucopenia, thrombocytopenia and pancytopenia) have been described in association with levetiracetam administration, generally at the beginning of the treatment. Complete blood cell counts are advised in patients experiencing important weakness, pyrexia, recurrent infections or coagulation disorders (section 4.8).

#### Suicide

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

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

#### Paediatric population

The tablet formulation is not adapted for use in infants and children under the age of 6 years.

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.

#### Excipients

Keppra 750 mg film-coated tablets contain E110 colouring agent which may cause allergic reactions.

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

#### Antiepileptic medicinal products

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

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 20 % higher levetiracetam clearance in children taking enzyme-inducing antiepileptic medicinal products. Dose adjustment is not required.

#### Probenecid

Probenecid (500 mg four times daily), a renal tubular secretion blocking agent, has been shown to inhibit the renal clearance of the primary metabolite, but not of levetiracetam. Nevertheless, the concentration of this metabolite remains low.

#### Methotrexate

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

#### Oral contraceptives and other pharmacokinetics interactions

Levetiracetam 1,000 mg daily did not influence the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel); endocrine parameters (luteinizing hormone and progesterone) were not modified. Levetiracetam 2,000 mg daily did not influence the pharmacokinetics of digoxin and warfarin; prothrombin times were not modified. Co-administration with digoxin, oral contraceptives and warfarin did not influence the pharmacokinetics of levetiracetam.

#### Laxatives

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

#### Food and alcohol

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

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

#### **4.6 Fertility, pregnancy and lactation**

##### Pregnancy

Postmarketing data from several prospective pregnancy registries have documented outcomes in over 1,000 women exposed to levetiracetam monotherapy during the first trimester of pregnancy. Overall, these data do not suggest a substantial increase in the risk for major congenital malformations, although a teratogenic risk cannot be completely excluded. Therapy with multiple antiepileptic medicinal products is associated with a higher risk of congenital malformations than monotherapy and, therefore, monotherapy should be considered. Studies in animals have shown reproductive toxicity (see section 5.3).

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

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.

##### Breastfeeding

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.

##### Fertility

No impact on fertility was detected in animal studies (see section 5.3). No clinical data are available, potential risk for human is unknown.

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

Levetiracetam has minor or moderate influence on the ability to drive and use machines. Due to possible different individual sensitivity, some patients might experience somnolence or other central nervous system related symptoms, especially at the beginning of treatment or following a dose increase. Therefore, caution is recommended in those patients when performing skilled tasks, *e.g.* driving vehicles or operating machinery. Patients are advised not to drive or use machines until it is established that their ability to perform such activities is not affected.

#### **4.8 Undesirable effects**

##### Summary of the safety profile

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

##### Tabulated list of adverse reactions

Adverse reactions reported in clinical studies (adults, adolescents, children and infants > 1 month) and from post-marketing experience are listed in the following table per System Organ Class and per frequency. Adverse reactions are presented in the order of decreasing seriousness and their frequency is defined as follows: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ) and very rare ( $< 1/10,000$ ).

<u>MedDRA SOC</u>	<u>Frequency category</u>			
	<u>Very common</u>	<u>Common</u>	<u>Uncommon</u>	<u>Rare</u>
<u>Infections and infestations</u>	Nasopharyngitis			Infection
<u>Blood and lymphatic system disorders</u>			Thrombocytopenia, leukopenia	Pancytopenia, neutropenia, agranulocytosis
<u>Immune system disorders</u>				Drug reaction with eosinophilia and systemic symptoms (DRESS), Hypersensitivity (including angioedema and anaphylaxis)
<u>Metabolism and nutrition disorders</u>		Anorexia	Weight decreased, weight increase	Hyponatraemia
<u>Psychiatric disorders</u>		Depression, hostility/aggression, anxiety, insomnia, nervousness/irritability	Suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusional state, panic attack, affect lability/mood swings, agitation	Completed suicide, personality disorder, thinking abnormal
<u>Nervous system disorders</u>	Somnolence, headache	Convulsion, balance disorder, dizziness, lethargy, tremor	Amnesia, memory impairment, coordination abnormal/ataxia, paraesthesia, disturbance in attention	Choreoathetosis, dyskinesia, hyperkinesia
<u>Eye disorders</u>			Diplopia, vision blurred	
<u>Ear and labyrinth disorders</u>		Vertigo		
<u>Respiratory, thoracic and mediastinal disorders</u>		Cough		
<u>Gastrointestinal disorders</u>		Abdominal pain, diarrhoea, dyspepsia, vomiting, nausea		Pancreatitis
<u>Hepatobiliary disorders</u>			Liver function test abnormal	Hepatic failure, hepatitis
<u>Renal and Urinary Disorders</u>				Acute Kidney injury

<u>MedDRA SOC</u>	<u>Frequency category</u>			
	<u>Very common</u>	<u>Common</u>	<u>Uncommon</u>	<u>Rare</u>
<u>Skin and subcutaneous tissue disorders</u>		Rash	Alopecia, eczema, pruritus,	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme
<u>Musculoskeletal and connective tissue disorders</u>			Muscular weakness, myalgia	Rhabdomyolysis and blood creatine phosphokinase increased*
<u>General disorders and administration site conditions</u>		Asthenia/fatigue		
<u>Injury, poisoning and procedural complications</u>			Injury	

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

Cases of encephalopathy have been rarely observed after levetiracetam administration. These undesirable effects generally occurred at the beginning of the treatment (few days to a few months) and were reversible after treatment discontinuation.

#### Description of selected adverse reactions

The risk of anorexia is higher when levetiracetam is coadministered with topiramate. In several cases of alopecia, recovery was observed when levetiracetam was discontinued. Bone marrow suppression was identified in some of the cases of pancytopenia.

#### Paediatric population

In patients aged 1 month to less than 4 years, a total of 190 patients have been treated with levetiracetam in placebo-controlled and open label extension studies. Sixty of these patients were treated with levetiracetam in placebo-controlled studies. In patients aged 4-16 years, a total of 645 patients have been treated with levetiracetam in placebo-controlled and open label extension studies. 233 of these patients were treated with levetiracetam in placebo-controlled studies. In both these paediatric age ranges, these data are supplemented with the post-marketing experience of the use of levetiracetam.

In addition, 101 infants aged less than 12 months have been exposed in a post authorization safety study. No new safety concerns for levetiracetam were identified for infants less than 12 months of age with epilepsy.

The adverse reaction profile of levetiracetam is generally similar across age groups and across the approved epilepsy indications. Safety results in paediatric patients in placebo-controlled clinical studies were consistent with the safety profile of levetiracetam in adults except for behavioural and psychiatric adverse reactions which were more common in children than in adults. In children and adolescents aged 4 to 16 years, vomiting (very common, 11.2%), agitation (common, 3.4%), mood swings (common, 2.1%), affect lability (common, 1.7%), aggression (common, 8.2%), abnormal behaviour (common, 5.6%), and lethargy (common, 3.9%) were reported more frequently than in other age ranges or in the overall safety profile. In infants and children aged 1 month to less than 4

years, irritability (very common, 11.7%) and coordination abnormal (common, 3.3%) were reported more frequently than in other age groups or in the overall safety profile.

A double-blind, placebo-controlled paediatric safety study with a non-inferiority design has assessed the cognitive and neuropsychological effects of levetiracetam in children 4 to 16 years of age with partial onset seizures. It was concluded that Keppra was not different (non inferior) from placebo with regard to the change from baseline of the Leiter-R Attention and Memory, Memory Screen Composite score in the per-protocol population. Results related to behavioural and emotional functioning indicated a worsening in levetiracetam treated patients on aggressive behaviour as measured in a standardised and systematic way using a validated instrument (CBCL – Achenbach Child Behavior Checklist). However subjects, who took levetiracetam in the long-term open label follow-up study, did not experience a worsening, on average, in their behavioural and emotional functioning; in particular measures of aggressive behaviour were not worse than baseline.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

### **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, other antiepileptics, ATC code: N03AX14.  
The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of  $\alpha$ -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. *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  $\text{Ca}^{2+}$  levels by partial inhibition of N-type  $\text{Ca}^{2+}$  currents and by reducing the release of  $\text{Ca}^{2+}$  from intraneuronal stores. In addition it partially reverses the reductions in GABA- and glycine-gated currents induced by zinc and  $\beta$ -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 efficacy and safety

*Adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents, children and infants from 1 month 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.

### Paediatric population

In paediatric 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.

In paediatric patients (1 month to less than 4 years of age), levetiracetam efficacy was established in a double-blind, placebo-controlled study, which included 116 patients and had a treatment duration of 5 days. In this study, patients were prescribed 20 mg/kg, 25 mg/kg, 40 mg/kg or 50 mg/kg daily dose of oral solution based on their age titration schedule. A dose of 20 mg/kg/day titrating to 40 mg/kg/day for infants one month to less than six months and a dose of 25 mg/kg/day titrating to 50 mg/kg/day for infants and children 6 months to less than 4 years old, was use in this study. The total daily dose was administered twice daily.

The primary measure of effectiveness was the responder rate (percent of patients with  $\geq 50$  % reduction from baseline in average daily partial onset seizure frequency) assessed by a blinded central reader using a 48-hour video EEG. The efficacy analysis consisted of 109 patients who had at least 24 hours of video EEG in both baseline and evaluation periods. 43.6 % of the levetiracetam treated patients and 19.6 % of the patients on placebo were considered as responders. The results are consistent across age group. With continued long-term treatment, 8.6 % of the patients were seizure-free for at least 6 months and 7.8 % were seizure-free for at least 1 year.

35 infants aged less than 1 year with partial onset seizures have been exposed in placebo-control clinical studies of which only 13 were aged < 6 months.

*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  $\mu\text{g/ml}$  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<sub>450</sub> 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<sub>450</sub> 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  $7 \pm 1$  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).

### 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).

### Paediatric population

#### *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).

In the population pharmacokinetic analysis conducted in patients from 1 month to 16 years of age, body weight was significantly correlated to apparent clearance (clearance increased with an increase in body weight) and apparent volume of distribution. Age also had an influence on both parameters. This effect was pronounced for the younger infants, and subsided as age increased, to become negligible around 4 years of age.

In both population pharmacokinetic analyses, there was about a 20 % increase of apparent clearance of levetiracetam when it was co-administered with an enzyme-inducing antiepileptic medicinal product.

### 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential.

Adverse effects not observed in clinical studies but seen in the rat and to a lesser extent in the mouse at exposure levels similar to human exposure levels and with possible relevance for clinical use were liver changes, indicating an adaptive response such as increased weight and centrilobular hypertrophy, fatty infiltration and increased liver enzymes in plasma.

No adverse reactions on male or female fertility or reproduction performance were observed in rats at doses up to 1800 mg/kg/day (x 6 the MRHD on a mg/m<sup>2</sup> or exposure basis) in parents and F1 generation.

Two embryo-foetal development (EFD) studies were performed in rats at 400, 1200 and 3600 mg/kg/day. At 3600 mg/kg/day, in only one of the 2 EFD studies, there was a slight decrease in foetal weight associated with a marginal increase in skeletal variations/minor anomalies. There was no effect on embryomortality and no increased incidence of malformations. The NOAEL (No Observed Adverse Effect Level) was 3600 mg/kg/day for pregnant female rats (x 12 the MRHD on a mg/m<sup>2</sup> basis) and 1200 mg/kg/day for fetuses.

Four embryo-foetal development studies were performed in rabbits covering doses of 200, 600, 800, 1200 and 1800 mg/kg/day. The dose level of 1800 mg/kg/day induced a marked maternal toxicity and a decrease in foetal weight associated with increased incidence of fetuses with cardiovascular/skeletal anomalies. The NOAEL was <200 mg/kg/day for the dams and 200 mg/kg/day for the fetuses (equal to the MRHD on a mg/m<sup>2</sup> basis).

A peri- and post-natal development study was performed in rats with levetiracetam doses of 70, 350 and 1800 mg/kg/day. The NOAEL was  $\geq$  1800 mg/kg/day for the F0 females, and for the survival, growth and development of the F1 offspring up to weaning (x 6 the MRHD on a mg/m<sup>2</sup> basis). Neonatal and juvenile animal studies in rats and dogs demonstrated that there were no adverse effects seen in any of the standard developmental or maturation endpoints at doses up to 1800 mg/kg/day (x 6-17 the MRHD on a mg/m<sup>2</sup> basis)

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

#### Tablet core:

Croscarmellose sodium  
Macrogol 6000  
Silica colloidal anhydrous.  
Magnesium stearate

#### Film-coating:

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**

This medicinal product does not require any special storage conditions.

### **6.5 Nature and contents of container**

Aluminium/PVC blisters placed into cardboard boxes containing 20, 30, 50, 60, 80, 100 film-coated tablets and multipacks containing 200 (2 packs of 100) film-coated tablets.

Aluminium/PVC perforated unit dose blisters placed into cardboard boxes containing 100 x 1 film-coated tablet.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7. MARKETING AUTHORISATION HOLDER**

UCB Pharma SA  
Allée de la Recherche 60  
B-1070 Brussels  
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  
EU/1/00/146/036

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 29 September 2000

Date of latest renewal: 20 August 2015

## **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

## 1. NAME OF THE MEDICINAL PRODUCT

Kepra 1000 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.

White, 19 mm oblong, scored and debossed with the code “ucb” and “1000” on one side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Kepra is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy.

Kepra is indicated as adjunctive therapy

- in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents, children and infants from 1 month 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

#### Posology

##### *Monotherapy for 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 for adults ( $\geq 18$ 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.

#### Discontinuation

If levetiracetam has to be discontinued it is recommended to withdraw it gradually (*e.g.* in adults and adolescents weighing more than 50 kg: 500 mg decreases twice daily every two to four weeks; in infants older than 6 months, children and adolescents weighing less than 50 kg: dose decrease should not exceed 10 mg/kg twice daily every two weeks; in infants (less than 6 months): dose decrease should not exceed 7 mg/kg twice daily every two weeks).

### Special populations

#### *Elderly (65 years and older)*

Adjustment of the dose is recommended in elderly patients with compromised renal function (see “Renal impairment” below).

#### *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, for adults and adolescents weighing 50 kg or more, the following formula:

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

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

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

Dosing adjustment for adult and adolescents patients weighing more than 50 kg with impaired renal function:

Group	Creatinine clearance (ml/min/1.73m <sup>2</sup> )	Dose and frequency
Normal	> 80	500 to 1,500 mg twice daily
Mild	50-79	500 to 1,000 mg twice daily
Moderate	30-49	250 to 750 mg twice daily
Severe	< 30	250 to 500 mg twice daily
End-stage renal disease patients undergoing dialysis <sup>(1)</sup>	-	500 to 1,000 mg once daily <sup>(2)</sup>

<sup>(1)</sup> A 750 mg loading dose is recommended on the first day of treatment with levetiracetam.

<sup>(2)</sup> 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.

The CLCr in ml/min/1.73 m<sup>2</sup> may be estimated from serum creatinine (mg/dl) determination, for young adolescents, children and infants, using the following formula (Schwartz formula):

$$\text{CLCr (ml/min/1.73 m}^2\text{)} = \frac{\text{Height (cm)} \times \text{ks}}{\text{Serum Creatinine (mg/dl)}}$$



ks= 0.45 in Term infants to 1 year old; ks= 0.55 in Children to less than 13 years and in adolescent female; ks= 0.7 in adolescent male

Dosing adjustment for infants, children and adolescents patients weighing less than 50 kg with impaired renal function:

Group	Creatinine clearance (ml/min/1.73m <sup>2</sup> )	Dose and frequency <sup>(1)</sup>	
		Infants 1 to less than 6 months	Infants 6 to 23 months, children and adolescents weighing less than 50 kg
Normal	> 80	7 to 21 mg/kg (0.07 to 0.21 ml/kg) twice daily	10 to 30 mg/kg (0.10 to 0.30 ml/kg) twice daily
Mild	50-79	7 to 14 mg/kg (0.07 to 0.14 ml/kg) twice daily	10 to 20 mg/kg (0.10 to 0.20 ml/kg) twice daily
Moderate	30-49	3.5 to 10.5 mg/kg (0.035 to 0.105 ml/kg) twice daily	5 to 15 mg/kg (0.05 to 0.15 ml/kg) twice daily
Severe	< 30	3.5 to 7 mg/kg (0.035 to 0.07 ml/kg) twice daily	5 to 10 mg/kg (0.05 to 0.10 ml/kg) twice daily
End-stage renal disease patients undergoing dialysis	--	7 to 14 mg/kg (0.07 to 0.14 ml/kg) once daily <sup>(2)</sup> <sup>(4)</sup>	10 to 20 mg/kg (0.10 to 0.20 ml/kg) once daily <sup>(3)</sup> <sup>(5)</sup>

<sup>(1)</sup> Keppra oral solution should be used for doses under 250 mg, for doses not multiple of 250 mg when dosing recommendation is not achievable by taking multiple tablets and for patients unable to swallow tablets.

<sup>(2)</sup> A 10.5 mg/kg (0.105 ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.

<sup>(3)</sup> A 15 mg/kg (0.15 ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.

<sup>(4)</sup> Following dialysis, a 3.5 to 7 mg/kg (0.035 to 0.07 ml/kg) supplemental dose is recommended.

<sup>(5)</sup> Following dialysis, a 5 to 10 mg/kg (0.05 to 0.10 ml/kg) supplemental dose is recommended.

### *Hepatic impairment*

No dose adjustment is needed in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the creatinine clearance may underestimate the renal insufficiency. Therefore a 50 % reduction of the daily maintenance dose is recommended when the creatinine clearance is < 60 ml/min/1.73 m<sup>2</sup>.

### Paediatric population

The physician should prescribe the most appropriate pharmaceutical form, presentation and strength according to age, weight and dose.

The tablet formulation is not adapted for use in infants and children under the age of 6 years. Keppra oral solution is the preferred formulation for use in this population. In addition, the available dose strengths of the tablets are not appropriate for initial treatment in children weighing less than 25 kg, for patients unable to swallow tablets or for the administration of doses below 250 mg. In all of the above cases Keppra oral solution should be used.

### *Monotherapy*

The safety and efficacy of Keppra in children and adolescents below 16 years as monotherapy treatment have not been established.

No data are available.

*Add-on therapy for infants aged 6 to 23 months, children (2 to 11 years) and adolescents (12 to 17 years) weighing less than 50 kg*

Keppra oral solution is the preferred formulation for use in infants and children under the age of 6 years.

For children 6 years and above, Keppra oral solution should be used for doses under 250 mg, for doses not multiple of 250 mg when dosing recommendation is not achievable by taking multiple tablets and for patients unable to swallow tablets

The lowest effective dose should be used. The starting dose for a child or adolescent of 25kg should be 250mg twice daily with a maximum dose of 750mg twice daily. Dose in children 50 kg or greater is the same as in adults.

*Add-on therapy for infants aged from 1 month to less than 6 months*

The oral solution is the formulation to use in infants.

#### 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.

### **4.3 Contraindications**

Hypersensitivity to the active substance or other pyrrolidone derivatives or to any of the excipients listed in section 6.1.

### **4.4 Special warnings and precautions for use**

#### Renal impairment

The administration of levetiracetam to patients with renal impairment may require dose adjustment. In patients with severely impaired hepatic function, assessment of renal function is recommended before dose selection (see section 4.2).

#### Acute Kidney injury

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

#### Blood cell counts

Rare cases of decreased blood cell counts (neutropenia, agranulocytosis, leucopenia, thrombocytopenia and pancytopenia) have been described in association with levetiracetam administration, generally at the beginning of the treatment. Complete blood cell counts are advised in patients experiencing important weakness, pyrexia, recurrent infections or coagulation disorders (section 4.8).

#### Suicide

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

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

### Paediatric population

The tablet formulation is not adapted for use in infants and children under the age of 6 years.

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.

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

### Antiepileptic medicinal products

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

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 20 % higher levetiracetam clearance in children taking enzyme-inducing antiepileptic medicinal products. Dose adjustment is not required.

### Probenecid

Probenecid (500 mg four times daily), a renal tubular secretion blocking agent, has been shown to inhibit the renal clearance of the primary metabolite, but not of levetiracetam. Nevertheless, the concentration of this metabolite remains low.

### Methotrexate

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

### Oral contraceptives and other pharmacokinetics interactions

Levetiracetam 1,000 mg daily did not influence the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel); endocrine parameters (luteinizing hormone and progesterone) were not modified. Levetiracetam 2,000 mg daily did not influence the pharmacokinetics of digoxin and warfarin; prothrombin times were not modified. Co-administration with digoxin, oral contraceptives and warfarin did not influence the pharmacokinetics of levetiracetam.

### Laxatives

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

### Food and alcohol

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

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

## **4.6 Fertility, pregnancy and lactation**

### Pregnancy

Postmarketing data from several prospective pregnancy registries have documented outcomes in over 1,000 women exposed to levetiracetam monotherapy during the first trimester of pregnancy. Overall,

these data do not suggest a substantial increase in the risk for major congenital malformations, although a teratogenic risk cannot be completely excluded. Therapy with multiple antiepileptic medicinal products is associated with a higher risk of congenital malformations than monotherapy and, therefore, monotherapy should be considered. Studies in animals have shown reproductive toxicity (see section 5.3).

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

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.

#### Breastfeeding

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.

#### Fertility

No impact on fertility was detected in animal studies (see section 5.3). No clinical data are available, potential risk for human is unknown.

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

Levetiracetam has minor or moderate influence on the ability to drive and use machines. Due to possible different individual sensitivity, some patients might experience somnolence or other central nervous system related symptoms, especially at the beginning of treatment or following a dose increase. Therefore, caution is recommended in those patients when performing skilled tasks, *e.g.* driving vehicles or operating machinery. Patients are advised not to drive or use machines until it is established that their ability to perform such activities is not affected.

### **4.8 Undesirable effects**

#### Summary of the safety profile

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

#### Tabulated list of adverse reactions

Adverse reactions reported in clinical studies (adults, adolescents, children and infants > 1 month) and from post-marketing experience are listed in the following table per System Organ Class and per frequency. Adverse reactions are presented in the order of decreasing seriousness and their frequency is defined as follows: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ) and very rare ( $< 1/10,000$ ).

<u>MedDRA SOC</u>	<u>Frequency category</u>			
	<u>Very common</u>	<u>Common</u>	<u>Uncommon</u>	<u>Rare</u>
<u>Infections and infestations</u>	Nasopharyngitis			Infection
<u>Blood and lymphatic system disorders</u>			Thrombocytopenia, leukopenia	Pancytopenia, neutropenia, agranulocytosis
<u>Immune system disorders</u>				Drug reaction with eosinophilia and systemic symptoms (DRESS), Hypersensitivity (including angioedema and anaphylaxis)
<u>Metabolism and nutrition disorders</u>		Anorexia	Weight decreased, weight increase	Hyponatraemia
<u>Psychiatric disorders</u>		Depression, hostility/aggression, anxiety, insomnia, nervousness/irritability	Suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusional state, panic attack, affect lability/mood swings, agitation	Completed suicide, personality disorder, thinking abnormal
<u>Nervous system disorders</u>	Somnolence, headache	Convulsion, balance disorder, dizziness, lethargy, tremor	Amnesia, memory impairment, coordination abnormal/ataxia, paraesthesia, disturbance in attention	Choreoathetosis, dyskinesia, hyperkinesia
<u>Eye disorders</u>			Diplopia, vision blurred	
<u>Ear and labyrinth disorders</u>		Vertigo		
<u>Respiratory, thoracic and mediastinal disorders</u>		Cough		
<u>Gastrointestinal disorders</u>		Abdominal pain, diarrhoea, dyspepsia, vomiting, nausea		Pancreatitis
<u>Hepatobiliary disorders</u>			Liver function test abnormal	Hepatic failure, hepatitis
<u>Renal and Urinary Disorders</u>				Acute Kidney injury
<u>Skin and subcutaneous tissue disorders</u>		Rash	Alopecia, eczema, pruritus,	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme

<u>MedDRA SOC</u>	<u>Frequency category</u>			
	<u>Very common</u>	<u>Common</u>	<u>Uncommon</u>	<u>Rare</u>
<u>Musculoskeletal and connective tissue disorders</u>			Muscular weakness, myalgia	Rhabdomyolysis and blood creatine phosphokinase increased*
<u>General disorders and administration site conditions</u>		Asthenia/fatigue		
<u>Injury, poisoning and procedural complications</u>			Injury	

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

Cases of encephalopathy have been rarely observed after levetiracetam administration. These undesirable effects generally occurred at the beginning of the treatment (few days to a few months) and were reversible after treatment discontinuation.

#### Description of selected adverse reactions

The risk of anorexia is higher when levetiracetam is coadministered with topiramate. In several cases of alopecia, recovery was observed when levetiracetam was discontinued. Bone marrow suppression was identified in some of the cases of pancytopenia.

#### Paediatric population

In patients aged 1 month to less than 4 years, a total of 190 patients have been treated with levetiracetam in placebo-controlled and open label extension studies. Sixty of these patients were treated with levetiracetam in placebo-controlled studies. In patients aged 4-16 years, a total of 645 patients have been treated with levetiracetam in placebo-controlled and open label extension studies. 233 of these patients were treated with levetiracetam in placebo-controlled studies. In both these paediatric age ranges, these data are supplemented with the post-marketing experience of the use of levetiracetam.

In addition, 101 infants aged less than 12 months have been exposed in a post authorization safety study. No new safety concerns for levetiracetam were identified for infants less than 12 months of age with epilepsy.

The adverse reaction profile of levetiracetam is generally similar across age groups and across the approved epilepsy indications. Safety results in paediatric patients in placebo-controlled clinical studies were consistent with the safety profile of levetiracetam in adults except for behavioural and psychiatric adverse reactions which were more common in children than in adults. In children and adolescents aged 4 to 16 years, vomiting (very common, 11.2%), agitation (common, 3.4%), mood swings (common, 2.1%), affect lability (common, 1.7%), aggression (common, 8.2%), abnormal behaviour (common, 5.6%), and lethargy (common, 3.9%) were reported more frequently than in other age ranges or in the overall safety profile. In infants and children aged 1 month to less than 4 years, irritability (very common, 11.7%) and coordination abnormal (common, 3.3%) were reported more frequently than in other age groups or in the overall safety profile.

A double-blind, placebo-controlled paediatric safety study with a non-inferiority design has assessed the cognitive and neuropsychological effects of levetiracetam in children 4 to 16 years of age with partial onset seizures. It was concluded that Keppra was not different (non inferior) from placebo with regard to the change from baseline of the Leiter-R Attention and Memory, Memory Screen Composite

score in the per-protocol population. Results related to behavioural and emotional functioning indicated a worsening in levetiracetam treated patients on aggressive behaviour as measured in a standardised and systematic way using a validated instrument (CBCL – Achenbach Child Behavior Checklist). However subjects, who took levetiracetam in the long-term open label follow-up study, did not experience a worsening, on average, in their behavioural and emotional functioning; in particular measures of aggressive behaviour were not worse than baseline.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## **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, other antiepileptics, ATC code: N03AX14. The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of  $\alpha$ -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. *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  $\text{Ca}^{2+}$  levels by partial inhibition of N-type  $\text{Ca}^{2+}$  currents and by reducing the release of  $\text{Ca}^{2+}$  from intraneuronal stores. In addition it partially reverses the reductions in GABA- and glycine-gated currents induced by zinc and  $\beta$ -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 efficacy and safety

*Adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents, children and infants from 1 month 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.

### Paediatric population

In paediatric 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.

In paediatric patients (1 month to less than 4 years of age), levetiracetam efficacy was established in a double-blind, placebo-controlled study, which included 116 patients and had a treatment duration of 5 days. In this study, patients were prescribed 20 mg/kg, 25 mg/kg, 40 mg/kg or 50 mg/kg daily dose of oral solution based on their age titration schedule. A dose of 20 mg/kg/day titrating to 40 mg/kg/day for infants one month to less than six months and a dose of 25 mg/kg/day titrating to 50 mg/kg/day for infants and children 6 months to less than 4 years old, was used in this study. The total daily dose was administered twice daily.

The primary measure of effectiveness was the responder rate (percent of patients with  $\geq 50$  % reduction from baseline in average daily partial onset seizure frequency) assessed by a blinded central reader using a 48-hour video EEG. The efficacy analysis consisted of 109 patients who had at least 24 hours of video EEG in both baseline and evaluation periods. 43.6 % of the levetiracetam treated patients and 19.6 % of the patients on placebo were considered as responders. The results are consistent across age group. With continued long-term treatment, 8.6 % of the patients were seizure-free for at least 6 months and 7.8 % were seizure-free for at least 1 year.

35 infants aged less than 1 year with partial onset seizures have been exposed in placebo-control clinical studies of which only 13 were aged < 6 months.

*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  $\mu\text{g/ml}$  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<sub>450</sub> 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<sub>450</sub> 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  $7 \pm 1$  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).

### 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).

### Paediatric population

#### *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).

In the population pharmacokinetic analysis conducted in patients from 1 month to 16 years of age, body weight was significantly correlated to apparent clearance (clearance increased with an increase in body weight) and apparent volume of distribution. Age also had an influence on both parameters. This effect was pronounced for the younger infants, and subsided as age increased, to become negligible around 4 years of age.

In both population pharmacokinetic analyses, there was about a 20 % increase of apparent clearance of levetiracetam when it was co-administered with an enzyme-inducing antiepileptic medicinal product.

### **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential.

Adverse effects not observed in clinical studies but seen in the rat and to a lesser extent in the mouse at exposure levels similar to human exposure levels and with possible relevance for clinical use were liver changes, indicating an adaptive response such as increased weight and centrilobular hypertrophy, fatty infiltration and increased liver enzymes in plasma.

No adverse reactions on male or female fertility or reproduction performance were observed in rats at doses up to 1800 mg/kg/day (x 6 the MRHD on a mg/m<sup>2</sup> or exposure basis) in parents and F1 generation.

Two embryo-foetal development (EFD) studies were performed in rats at 400, 1200 and 3600 mg/kg/day. At 3600 mg/kg/day, in only one of the 2 EFD studies, there was a slight decrease in foetal weight associated with a marginal increase in skeletal variations/minor anomalies. There was no effect on embryomortality and no increased incidence of malformations. The NOAEL (No Observed Adverse Effect Level) was 3600 mg/kg/day for pregnant female rats (x 12 the MRHD on a mg/m<sup>2</sup> basis) and 1200 mg/kg/day for fetuses.

Four embryo-foetal development studies were performed in rabbits covering doses of 200, 600, 800, 1200 and 1800 mg/kg/day. The dose level of 1800 mg/kg/day induced a marked maternal toxicity and a decrease in foetal weight associated with increased incidence of fetuses with cardiovascular/skeletal anomalies. The NOAEL was <200 mg/kg/day for the dams and 200 mg/kg/day for the fetuses (equal to the MRHD on a mg/m<sup>2</sup> basis).

A peri- and post-natal development study was performed in rats with levetiracetam doses of 70, 350 and 1800 mg/kg/day. The NOAEL was ≥ 1800 mg/kg/day for the F0 females, and for the survival, growth and development of the F1 offspring up to weaning (x 6 the MRHD on a mg/m<sup>2</sup> basis).

Neonatal and juvenile animal studies in rats and dogs demonstrated that there were no adverse effects seen in any of the standard developmental or maturation endpoints at doses up to 1800 mg/kg/day (x 6-17 the MRHD on a mg/m<sup>2</sup> basis)

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Tablet core:

Croscarmellose sodium  
Macrogol 6000  
Silica colloidal anhydrous  
Magnesium stearate

#### Film-coating:

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**

This medicinal product does not require any special storage conditions.

## **6.5 Nature and contents of container**

Aluminium/PVC blisters placed into cardboard boxes containing 10, 20, 30, 50, 60, 100 film-coated tablets and multipacks containing 200 (2 packs of 100) film-coated tablets.

Aluminium/PVC perforated unit dose blisters placed into cardboard boxes containing 100 x 1 film-coated tablet.

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7. MARKETING AUTHORISATION HOLDER**

UCB Pharma SA  
Allée de la Recherche 60  
B-1070 Brussels  
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  
EU/1/00/146/037

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 29 September 2000

Date of latest renewal: 20 August 2015

## **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

## 1. NAME OF THE MEDICINAL PRODUCT

Keppra 100 mg/ml oral solution

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 mg levetiracetam

### Excipients with known effect:

Each ml contains 2.7 mg of methyl parahydroxybenzoate (E218), 0.3 mg of propyl parahydroxybenzoate (E216) and 300 mg of maltitol liquid.

For the 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 adults and adolescents 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, adolescents, children and infants from 1 month 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

#### Posology

#### *Monotherapy for 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 for adults ( $\geq 18$ 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.

### Discontinuation

If levetiracetam has to be discontinued it is recommended to withdraw it gradually (*e.g.* in adults and adolescents weighing more than 50 kg: 500 mg decreases twice daily every two to four weeks; in infants older than 6 months, children and adolescents weighting less than 50 kg: dose decrease should not exceed 10 mg/kg twice daily every two weeks; in infants (less than 6 months): dose decrease should not exceed 7 mg/ kg twice daily every two weeks).

### Special populations

#### *Elderly (65 years and older)*

Adjustment of the dose is recommended in elderly patients with compromised renal function (see “Renal impairment” below).

#### *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, for adults and adolescents weighting 50 kg or more, the following formula:

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

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

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

Dosing adjustment for adult and adolescents patients weighing more than 50 kg with impaired renal function:

Group	Creatinine clearance (ml/min/1.73m <sup>2</sup> )	Dose and frequency
Normal	> 80	500 to 1,500 mg twice daily
Mild	50-79	500 to 1,000 mg twice daily
Moderate	30-49	250 to 750 mg twice daily
Severe	< 30	250 to 500 mg twice daily
End-stage renal disease patients undergoing dialysis <sup>(1)</sup>	-	500 to 1,000 mg once daily <sup>(2)</sup>

<sup>(1)</sup> A 750 mg loading dose is recommended on the first day of treatment with levetiracetam.

<sup>(2)</sup> 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.

The CLcr in ml/min/1.73 m<sup>2</sup> may be estimated from serum creatinine (mg/dl) determination, for young adolescents, children and infants, using the following formula (Schwartz formula):

$$\text{CLcr (ml/min/1.73 m}^2\text{)} = \frac{\text{Height (cm)} \times \text{ks}}{\text{Serum Creatinine (mg/dl)}}$$

ks= 0.45 in Term infants to 1 year old; ks= 0.55 in Children to less than 13 years and in adolescent female; ks= 0.7 in adolescent male

Dosing adjustment for infants, children and adolescents patients weighing less than 50 kg with impaired renal function:

Group	Creatinine clearance (ml/min/1.73m <sup>2</sup> )	Dose and frequency <sup>(1)</sup>	
		Infants 1 to less than 6 months	Infants 6 to 23 months, children and adolescents weighing less than 50 kg
Normal	> 80	7 to 21 mg/kg (0.07 to 0.21 ml/kg) twice daily	10 to 30 mg/kg (0.10 to 0.30 ml/kg) twice daily
Mild	50-79	7 to 14 mg/kg (0.07 to 0.14 ml/kg) twice daily	10 to 20 mg/kg (0.10 to 0.20 ml/kg) twice daily
Moderate	30-49	3.5 to 10.5 mg/kg (0.035 to 0.105 ml/kg) twice daily	5 to 15 mg/kg (0.05 to 0.15 ml/kg) twice daily
Severe	< 30	3.5 to 7 mg/kg (0.035 to 0.07 ml/kg) twice daily	5 to 10 mg/kg (0.05 to 0.10 ml/kg) twice daily
End-stage renal disease patients undergoing dialysis	--	7 to 14 mg/kg (0.07 to 0.14 ml/kg) once daily <sup>(2)</sup> <sup>(4)</sup>	10 to 20 mg/kg (0.10 to 0.20 ml/kg) once daily <sup>(3)</sup> <sup>(5)</sup>

<sup>(1)</sup> Keppra oral solution should be used for doses under 250 mg, for doses not multiple of 250 mg when dosing recommendation is not achievable by taking multiple tablets and for patients unable to swallow tablets.

<sup>(2)</sup> A 10.5 mg/kg (0.105 ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.

<sup>(3)</sup> A 15 mg/kg (0.15 ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.

<sup>(4)</sup> Following dialysis, a 3.5 to 7 mg/kg (0.035 to 0.07 ml/kg) supplemental dose is recommended.

<sup>(5)</sup> Following dialysis, a 5 to 10 mg/kg (0.05 to 0.10 ml/kg) supplemental dose is recommended.

### *Hepatic impairment*

No dose adjustment is needed in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the creatinine clearance may underestimate the renal insufficiency. Therefore a 50 % reduction of the daily maintenance dose is recommended when the creatinine clearance is < 60 ml/min/1.73 m<sup>2</sup>.

### Paediatric population

The physician should prescribe the most appropriate pharmaceutical form, presentation and strength according to age, weight and dose.

Keppra oral solution is the preferred formulation for use in infants and children under the age of 6 years. In addition, the available dose strengths of the tablets are not appropriate for initial treatment in children weighing less than 25 kg, for patients unable to swallow tablets or for the administration of doses below 250 mg. In all of the above cases Keppra oral solution should be used.

### *Monotherapy*



The safety and efficacy of Keppra in children and adolescents below 16 years as monotherapy treatment have not been established.

No data are available.

*Add-on therapy for infants aged 6 to 23 months, children (2 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.

Dose in children 50 kg or greater is the same as in adults.

Dose recommendations for infants from 6 months of age, children and adolescents:

Weight	Starting dose: 10 mg/kg twice daily	Maximum dose: 30 mg/kg twice daily
6 kg <sup>(1)</sup>	60 mg (0.6 ml) twice daily	180 mg (1.8 ml) twice daily
10 kg <sup>(1)</sup>	100 mg (1 ml) twice daily	300 mg (3 ml) twice daily
15 kg <sup>(1)</sup>	150 mg (1.5 ml) twice daily	450 mg (4.5 ml) twice daily
20 kg <sup>(1)</sup>	200 mg (2 ml) twice daily	600 mg (6 ml) twice daily
25 kg	250 mg twice daily	750 mg twice daily
From 50 kg <sup>(2)</sup>	500 mg twice daily	1,500 mg twice daily

<sup>(1)</sup> Children 25 kg or less should preferably start the treatment with Keppra 100 mg/ml oral solution.

<sup>(2)</sup> Dose in children and adolescents 50 kg or more is the same as in adults.

*Add-on therapy for infants aged from 1 month to less than 6 months*

The initial therapeutic dose is 7 mg/kg twice daily.

Depending upon the clinical response and tolerability, the dose can be increased up to 21 mg/kg twice daily. Dose changes should not exceed increases or decreases of 7 mg/kg twice daily every two weeks. The lowest effective dose should be used.

Infants should start the treatment with Keppra 100 mg/ml oral solution.

Dose recommendations for infants aged from 1 month to less than 6 months:

Weight	Starting dose: 7 mg/kg twice daily	Maximum dose: 21 mg/kg twice daily
4 kg	28 mg (0.3 ml) twice daily	84 mg (0.85 ml) twice daily
5 kg	35 mg (0.35 ml) twice daily	105 mg (1.05 ml) twice daily
7 kg	49 mg (0.5 ml) twice daily	147 mg (1.5 ml) twice daily

Three presentations are available:

- A 300 ml bottle with a 10 ml oral syringe (delivering up to 1000 mg levetiracetam) graduated every 0.25 ml (corresponding to 25 mg).  
This presentation should be prescribed for children aged 4 years and older, adolescents and adults.
- A 150 ml bottle with a 3 ml oral syringe (delivering up to 300 mg levetiracetam) graduated every 0.1 ml (corresponding to 10 mg)  
In order to ensure the accuracy of the dosing, this presentation should be prescribed for infants and young children aged from 6 months to less than 4 years.
- A 150 ml bottle with a 1 ml oral syringe (delivering up to 100 mg levetiracetam) graduated every 0.05 ml (corresponding to 5 mg)

In order to ensure the accuracy of the dosing, this presentation should be prescribed for infants aged 1 month to less than 6 months.

#### Method of administration

The oral solution may be diluted in a glass of water or baby's bottle and may be taken with or without food.

### **4.3 Contraindications**

Hypersensitivity to the active substance or other pyrrolidone derivatives or to any of the excipients listed in section 6.1.

### **4.4 Special warnings and precautions for use**

#### Renal impairment

The administration of levetiracetam to patients with renal impairment may require dose adjustment. In patients with severely impaired hepatic function, assessment of renal function is recommended before dose selection (see section 4.2).

#### Acute Kidney injury

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

#### Blood cell counts

Rare cases of decreased blood cell counts (neutropenia, agranulocytosis, leucopenia, thrombocytopenia and pancytopenia) have been described in association with levetiracetam administration, generally at the beginning of the treatment. Complete blood cell counts are advised in patients experiencing important weakness, pyrexia, recurrent infections or coagulation disorders (section 4.8).

#### Suicide

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

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

#### Paediatric population

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.

#### Excipients

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

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

#### Antiepileptic medicinal products

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

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 20 % higher levetiracetam clearance in children taking enzyme-inducing antiepileptic medicinal products. Dose adjustment is not required.

#### Probenecid

Probenecid (500 mg four times daily), a renal tubular secretion blocking agent, has been shown to inhibit the renal clearance of the primary metabolite, but not of levetiracetam. Nevertheless, the concentration of this metabolite remains low.

#### Methotrexate

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

#### Oral contraceptives and other pharmacokinetics interactions

Levetiracetam 1,000 mg daily did not influence the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel); endocrine parameters (luteinizing hormone and progesterone) were not modified. Levetiracetam 2,000 mg daily did not influence the pharmacokinetics of digoxin and warfarin; prothrombin times were not modified. Co-administration with digoxin, oral contraceptives and warfarin did not influence the pharmacokinetics of levetiracetam.

#### Laxatives

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

#### Food and alcohol

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

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

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

Postmarketing data from several prospective pregnancy registries have documented outcomes in over 1,000 women exposed to levetiracetam monotherapy during the first trimester of pregnancy. Overall, these data do not suggest a substantial increase in the risk for major congenital malformations, although a teratogenic risk cannot be completely excluded. Therapy with multiple antiepileptic medicinal products is associated with a higher risk of congenital malformations than monotherapy and, therefore, monotherapy should be considered. Studies in animals have shown reproductive toxicity (see section 5.3).

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

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.

#### Breastfeeding

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.

#### Fertility

No impact on fertility was detected in animal studies (see section 5.3). No clinical data are available, potential risk for human is unknown.

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

Levetiracetam has minor or moderate influence on the ability to drive and use machines. Due to possible different individual sensitivity, some patients might experience somnolence or other central nervous system related symptoms, especially at the beginning of treatment or following a dose increase. Therefore, caution is recommended in those patients when performing skilled tasks, *e.g.* driving vehicles or operating machinery. Patients are advised not to drive or use machines until it is established that their ability to perform such activities is not affected.

### **4.8 Undesirable effects**

#### Summary of the safety profile

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

#### Tabulated list of adverse reactions

Adverse reactions reported in clinical studies (adults, adolescents, children and infants > 1 month) and from post-marketing experience are listed in the following table per System Organ Class and per frequency. Adverse reactions are presented in the order of decreasing seriousness and their frequency is defined as follows: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ) and very rare ( $< 1/10,000$ ).

<u>MedDRA SOC</u>	<u>Frequency category</u>			
	<u>Very common</u>	<u>Common</u>	<u>Uncommon</u>	<u>Rare</u>
<u>Infections and infestations</u>	Nasopharyngitis			Infection
<u>Blood and lymphatic system disorders</u>			Thrombocytopenia, leukopenia	Pancytopenia, neutropenia, agranulocytosis

<u>MedDRA SOC</u>	<u>Frequency category</u>			
	<u>Very common</u>	<u>Common</u>	<u>Uncommon</u>	<u>Rare</u>
<u>Immune system disorders</u>				Drug reaction with eosinophilia and systemic symptoms (DRESS), Hypersensitivity (including angioedema and anaphylaxis)
<u>Metabolism and nutrition disorders</u>		Anorexia	Weight decreased , weight increase	Hyponatraemia
<u>Psychiatric disorders</u>		Depression, hostility/ aggression, anxiety, insomnia, nervousness/irritability	Suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusional state , panic attack, affect lability/mood swings, agitation	Completed suicide, personality disorder, thinking abnormal
<u>Nervous system disorders</u>	Somnolence, headache	Convulsion, balance disorder, dizziness, lethargy, tremor	Amnesia, memory impairment, coordination abnormal/ataxia, paraesthesia, disturbance in attention	Choreoathetosis, dyskinesia, hyperkinesia
<u>Eye disorders</u>			Diplopia, vision blurred	
<u>Ear and labyrinth disorders</u>		Vertigo		
<u>Respiratory, thoracic and mediastinal disorders</u>		Cough		
<u>Gastrointestinal disorders</u>		Abdominal pain, diarrhoea, dyspepsia, vomiting, nausea		Pancreatitis
<u>Hepatobiliary disorders</u>			Liver function test abnormal	Hepatic failure, hepatitis
<u>Renal and Urinary Disorders</u>				Acute Kidney injury
<u>Skin and subcutaneous tissue disorders</u>		Rash	Alopecia, eczema, pruritus,	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme
<u>Musculoskeletal and connective tissue disorders</u>			Muscular weakness, myalgia	Rhabdomyolysis and blood creatine phosphokinase increased*

<u>MedDRA SOC</u>	<u>Frequency category</u>			
	<u>Very common</u>	<u>Common</u>	<u>Uncommon</u>	<u>Rare</u>
<u>General disorders and administration site conditions</u>		Asthenia/fatigue		
<u>Injury, poisoning and procedural complications</u>			Injury	

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

Cases of encephalopathy have been rarely observed after levetiracetam administration. These undesirable effects generally occurred at the beginning of the treatment (few days to a few months) and were reversible after treatment discontinuation.

#### Description of selected adverse reactions

The risk of anorexia is higher when levetiracetam is coadministered with topiramate. In several cases of alopecia, recovery was observed when levetiracetam was discontinued. Bone marrow suppression was identified in some of the cases of pancytopenia.

#### Paediatric population

In patients aged 1 month to less than 4 years, a total of 190 patients have been treated with levetiracetam in placebo-controlled and open label extension studies. Sixty of these patients were treated with levetiracetam in placebo-controlled studies. In patients aged 4-16 years, a total of 645 patients have been treated with levetiracetam in placebo-controlled and open label extension studies. 233 of these patients were treated with levetiracetam in placebo-controlled studies. In both these paediatric age ranges, these data are supplemented with the post-marketing experience of the use of levetiracetam.

In addition, 101 infants aged less than 12 months have been exposed in a post authorization safety study. No new safety concerns for levetiracetam were identified for infants less than 12 months of age with epilepsy.

The adverse reaction profile of levetiracetam is generally similar across age groups and across the approved epilepsy indications. Safety results in paediatric patients in placebo-controlled clinical studies were consistent with the safety profile of levetiracetam in adults except for behavioural and psychiatric adverse reactions which were more common in children than in adults. In children and adolescents aged 4 to 16 years, vomiting (very common, 11.2%), agitation (common, 3.4%), mood swings (common, 2.1%), affect lability (common, 1.7%), aggression (common, 8.2%), abnormal behaviour (common, 5.6%), and lethargy (common, 3.9%) were reported more frequently than in other age ranges or in the overall safety profile. In infants and children aged 1 month to less than 4 years, irritability (very common, 11.7%) and coordination abnormal (common, 3.3%) were reported more frequently than in other age groups or in the overall safety profile.

A double-blind, placebo-controlled paediatric safety study with a non-inferiority design has assessed the cognitive and neuropsychological effects of levetiracetam in children 4 to 16 years of age with partial onset seizures. It was concluded that Keppra was not different (non inferior) from placebo with regard to the change from baseline of the Leiter-R Attention and Memory, Memory Screen Composite score in the per-protocol population. Results related to behavioural and emotional functioning indicated a worsening in levetiracetam treated patients on aggressive behaviour as measured in a standardised and systematic way using a validated instrument (CBCL – Achenbach Child Behavior Checklist). However subjects, who took levetiracetam in the long-term open label follow-up study,

did not experience a worsening, on average, in their behavioural and emotional functioning; in particular measures of aggressive behaviour were not worse than baseline.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system listed in Appendix V**.

## **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, other antiepileptics, ATC code: N03AX14

The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of  $\alpha$ -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. *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  $\beta$ -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 efficacy and safety

### *Adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents, children and infants from 1 month 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.

### Paediatric population

In paediatric 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.

In paediatric patients (1 month to less than 4 years of age), levetiracetam efficacy was established in a double-blind, placebo-controlled study, which included 116 patients and had a treatment duration of 5 days. In this study, patients were prescribed 20 mg/kg, 25 mg/kg, 40 mg/kg or 50 mg/kg daily dose of oral solution based on their age titration schedule. A dose of 20 mg/kg/day titrating to 40 mg/kg/day for infants one month to less than six months and a dose of 25 mg/kg/day titrating to 50 mg/kg/day for infants and children 6 months to less than 4 years old, was used in this study. The total daily dose was administered twice daily.

The primary measure of effectiveness was the responder rate (percent of patients with  $\geq 50\%$  reduction from baseline in average daily partial onset seizure frequency) assessed by a blinded central reader using a 48-hour video EEG. The efficacy analysis consisted of 109 patients who had at least 24 hours of video EEG in both baseline and evaluation periods. 43.6 % of the levetiracetam treated patients and 19.6 % of the patients on placebo were considered as responders. The results are consistent across age group. With continued long-term treatment, 8.6 % of the patients were seizure-free for at least 6 months and 7.8 % were seizure-free for at least 1 year.

35 infants aged less than 1 year with partial onset seizures have been exposed in placebo-control clinical studies of which only 13 were aged < 6 months.

### *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  $\mu\text{g/ml}$  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<sub>450</sub> 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<sub>450</sub> 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).

### 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).

### Paediatric population

#### *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).

In the population pharmacokinetic analysis conducted in patients from 1 month to 16 years of age, body weight was significantly correlated to apparent clearance (clearance increased with an increase in body weight) and apparent volume of distribution. Age also had an influence on both parameters. This effect was pronounced for the younger infants, and subsided as age increased, to become negligible around 4 years of age.

In both population pharmacokinetic analyses, there was about a 20 % increase of apparent clearance of levetiracetam when it was co-administered with an enzyme-inducing antiepileptic medicinal product.

## **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential.

Adverse effects not observed in clinical studies but seen in the rat and to a lesser extent in the mouse at exposure levels similar to human exposure levels and with possible relevance for clinical use were liver changes, indicating an adaptive response such as increased weight and centrilobular hypertrophy, fatty infiltration and increased liver enzymes in plasma.

No adverse reactions on male or female fertility or reproduction performance were observed in rats at doses up to 1800 mg/kg/day (x 6 the MRHD on a mg/m<sup>2</sup> or exposure basis) in parents and F1 generation.

Two embryo-foetal development (EFD) studies were performed in rats at 400, 1200 and 3600 mg/kg/day. At 3600 mg/kg/day, in only one of the 2 EFD studies, there was a slight decrease in foetal weight associated with a marginal increase in skeletal variations/minor anomalies. There was no effect on embryomortality and no increased incidence of malformations. The NOAEL (No Observed Adverse Effect Level) was 3600 mg/kg/day for pregnant female rats (x 12 the MRHD on a mg/m<sup>2</sup> basis) and 1200 mg/kg/day for fetuses.

Four embryo-foetal development studies were performed in rabbits covering doses of 200, 600, 800, 1200 and 1800 mg/kg/day. The dose level of 1800 mg/kg/day induced a marked maternal toxicity and a decrease in foetal weight associated with increased incidence of fetuses with cardiovascular/skeletal anomalies. The NOAEL was <200 mg/kg/day for the dams and 200 mg/kg/day for the fetuses (equal to the MRHD on a mg/m<sup>2</sup> basis).

A peri- and post-natal development study was performed in rats with levetiracetam doses of 70, 350 and 1800 mg/kg/day. The NOAEL was  $\geq$  1800 mg/kg/day for the F0 females, and for the survival, growth and development of the F1 offspring up to weaning (x 6 the MRHD on a mg/m<sup>2</sup> basis).

Neonatal and juvenile animal studies in rats and dogs demonstrated that there were no adverse effects seen in any of the standard developmental or maturation endpoints at doses up to 1800 mg/kg/day (x 6- 17 the MRHD on a mg/m<sup>2</sup> basis)

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

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

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.  
After first opening: 7 months

### **6.4 Special precautions for storage**

Store in the original bottle in order to protect from light.

### **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 10 ml graduated oral syringe (polypropylene, polyethylene) and an adaptor for the syringe (polyethylene).

150 ml amber glass bottle (type III) with a white child resistant closure (polypropylene) in a cardboard box also containing a 3 ml graduated oral syringe (polypropylene, polyethylene) and an adaptor for the syringe (polyethylene).

150 ml amber glass bottle (type III) with a white child resistant closure (polypropylene) in a cardboard box also containing a 1 ml graduated oral syringe (polypropylene, polyethylene) and an adaptor for the syringe (polyethylene).

#### **6.6 Special precautions for disposal**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

### **7. MARKETING AUTHORISATION HOLDER**

UCB Pharma SA  
Allée de la Recherche 60  
B-1070 Brussels  
Belgium

### **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/00/146/027  
EU/1/00/146/031  
EU/1/00/146/032

### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 29 September 2000  
Date of latest renewal: 20 August 2015

### **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

## 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.

Each 5 ml vial contains 500 mg of levetiracetam.

### Excipient with known effect:

Each vial contains 19 mg of sodium.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear, colourless, 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 adults and adolescents 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, adolescents 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

#### Posology

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.

#### *Monotherapy for 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 for 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.

#### Duration of treatment

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

#### Discontinuation

If levetiracetam has to be discontinued it is recommended to withdraw it gradually (*e.g.* in adults and adolescents weighing more than 50 kg: 500 mg decreases twice daily every two to four weeks; in children and adolescents weighing less than 50 kg: dose decrease should not exceed 10 mg/kg twice daily every two weeks).

#### Special populations

##### *Elderly (65 years and older)*

Adjustment of the dose is recommended in elderly patients with compromised renal function (see “Renal impairment” below).

##### *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 (CL<sub>cr</sub>) in ml/min is needed. The CL<sub>cr</sub> in ml/min may be estimated from serum creatinine (mg/dl) determination, for adults and adolescents weighing 50 kg or more, the following formula:

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

Then CL<sub>cr</sub> is adjusted for body surface area (BSA) as follows:

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

Dosing adjustment for adult and adolescents patients weighing more than 50 kg with impaired renal function:

Group	Creatinine clearance (ml/min/1.73m <sup>2</sup> )	Dose and frequency
Normal	> 80	500 to 1,500 mg twice daily
Mild	50-79	500 to 1,000 mg twice daily
Moderate	30-49	250 to 750 mg twice daily
Severe	< 30	250 to 500 mg twice daily
End-stage renal disease patients undergoing dialysis <sup>(1)</sup>	-	500 to 1,000 mg once daily <sup>(2)</sup>

<sup>(1)</sup> A 750 mg loading dose is recommended on the first day of treatment with levetiracetam.

<sup>(2)</sup> 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.

The CL<sub>CR</sub> in ml/min/1.73 m<sup>2</sup> may be estimated from serum creatinine (mg/dl) determination, for young adolescents and children using the following formula (Schwartz formula):

$$\text{CL}_{\text{CR}} (\text{ml}/\text{min}/1.73 \text{ m}^2) = \frac{\text{Height (cm)} \times \text{ks}}{\text{Serum Creatinine (mg/dl)}}$$

ks= 0.55 in Children to less than 13 years and in adolescent female; ks= 0.7 in adolescent male

Dosing adjustment for children and adolescents patients weighing less than 50 kg with impaired renal function:

Group	Creatinine clearance (ml/min/1.73m <sup>2</sup> )	Dose and frequency
		Children from 4 years and adolescents weighing less than 50 kg
Normal	> 80	10 to 30 mg/kg (0.10 to 0.30 ml/kg) twice daily
Mild	50-79	10 to 20 mg/kg (0.10 to 0.20 ml/kg) twice daily
Moderate	30-49	5 to 15 mg/kg (0.05 to 0.15 ml/kg) twice daily
Severe	< 30	5 to 10 mg/kg (0.05 to 0.10 ml/kg) twice daily
End-stage renal disease patients undergoing dialysis	--	10 to 20 mg/kg (0.10 to 0.20 ml/kg) once daily <sup>(1)(2)</sup>

<sup>(1)</sup> A 15 mg/kg (0.15 ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.

<sup>(2)</sup> Following dialysis, a 5 to 10 mg/kg (0.05 to 0.10 ml/kg) supplemental dose is recommended.

### *Hepatic impairment*

No dose adjustment is needed in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the creatinine clearance may underestimate the renal insufficiency. Therefore a 50 % reduction of the daily maintenance dose is recommended when the creatinine clearance is < 60 ml/min/1.73 m<sup>2</sup>.

### Paediatric population

The physician should prescribe the most appropriate pharmaceutical form, presentation and strength according to age, weight and dose.

### *Monotherapy*

The safety and efficacy of Keppra in children below and adolescents 16 years as monotherapy treatment have not been established. No data are available.

### *Add-on therapy for 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.

Dose in children 50 kg or greater is the same as in adults.



Dose recommendations for children and adolescents:

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

<sup>(1)</sup> Children 25 kg or less should preferably start the treatment with Keppra 100 mg/ml oral solution.

<sup>(2)</sup> Dose in children and adolescents 50 kg or more is the same as in adults.

#### *Add-on therapy for infants and children less than 4 years*

The safety and efficacy of Keppra concentrate for solution for infusion in infants and children less than 4 years have not been established.

Currently available data are described in sections 4.8, 5.1, and 5.2 but no recommendation on a posology can be made.

#### Method of administration

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).

### **4.3 Contraindications**

Hypersensitivity to the active substance or other pyrrolidone derivatives or to any of the excipients listed in section 6.1.

### **4.4 Special warnings and precautions for use**

#### Renal impairment

The administration of levetiracetam to patients with renal impairment may require dose adjustment. In patients with severely impaired hepatic function, assessment of renal function is recommended before dose selection (see section 4.2).

#### Acute Kidney injury

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

#### Blood cell counts

Rare cases of decreased blood cell counts (neutropenia, agranulocytosis, leucopenia, thrombocytopenia and pancytopenia) have been described in association with levetiracetam administration, generally at the beginning of the treatment. Complete blood cell counts are advised in patients experiencing important weakness, pyrexia, recurrent infections or coagulation disorders (section 4.8).

#### Suicide

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

Therefore patients should be monitored for signs of depression and/or suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients)

should be advised to seek medical advice should signs of depression and/or suicidal ideation or behaviour emerge.

#### Paediatric population

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.

#### Excipients

This medicinal product contains 2.5 mmol (or 57 mg) sodium per maximum single dose (0.8 mmol (or 19 mg) 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**

#### Antiepileptic medicinal products

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

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 20 % higher levetiracetam clearance in children taking enzyme-inducing antiepileptic medicinal products. Dose adjustment is not required.

#### Probenecid

Probenecid (500 mg four times daily), a renal tubular secretion blocking agent, has been shown to inhibit the renal clearance of the primary metabolite, but not of levetiracetam. Nevertheless, the concentration of this metabolite remains low.

#### Methotrexate

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

#### Oral contraceptives and other pharmacokinetics interactions

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.

#### Alcohol

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

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

Postmarketing data from several prospective pregnancy registries have documented outcomes in over 1,000 women exposed to levetiracetam monotherapy during the first trimester of pregnancy. Overall, these data do not suggest a substantial increase in the risk for major congenital malformations, although a teratogenic risk cannot be completely excluded. Therapy with multiple antiepileptic

medicinal products is associated with a higher risk of congenital malformations than monotherapy and, therefore, monotherapy should be considered. Studies in animals have shown reproductive toxicity (see section 5.3).

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

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.

#### Breastfeeding

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.

#### Fertility

No impact on fertility was detected in animal studies (see section 5.3). No clinical data are available, potential risk for human is unknown.

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

Levetiracetam has minor or moderate influence on the ability to drive and use machines. Due to possible different individual sensitivity, some patients might experience somnolence or other central nervous system related symptoms, especially at the beginning of treatment or following a dose increase. Therefore, caution is recommended in those patients when performing skilled tasks, *e.g.* driving vehicles or operating machinery. Patients are advised not to drive or use machines until it is established that their ability to perform such activities is not affected.

### **4.8 Undesirable effects**

#### Summary of the safety profile

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

#### Tabulated list of adverse reactions

Adverse reactions reported in clinical studies (adults, adolescents, children and infants > 1 month) and from post-marketing experience are listed in the following table per System Organ Class and per frequency. Adverse reactions are presented in the order of decreasing seriousness and their frequency is defined as follows: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ) and very rare ( $< 1/10,000$ ).

<u>MedDRA SOC</u>	<u>Frequency category</u>			
	<u>Very common</u>	<u>Common</u>	<u>Uncommon</u>	<u>Rare</u>
<u>Infections and infestations</u>	Nasopharyngitis			Infection

<u>MedDRA SOC</u>	<u>Frequency category</u>			
	<u>Very common</u>	<u>Common</u>	<u>Uncommon</u>	<u>Rare</u>
<u>Blood and lymphatic system disorders</u>			Thrombocytopenia, leukopenia	Pancytopenia, neutropenia, agranulocytosis
<u>Immune system disorders</u>				Drug reaction with eosinophilia and systemic symptoms (DRESS), Hypersensitivity (including angioedema and anaphylaxis)
<u>Metabolism and nutrition disorders</u>		Anorexia	Weight decreased, weight increase	Hyponatraemia
<u>Psychiatric disorders</u>		Depression, hostility/aggression, anxiety, insomnia, nervousness/irritability	Suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusional state, panic attack, affect lability/mood swings, agitation	Completed suicide, personality disorder, thinking abnormal
<u>Nervous system disorders</u>	Somnolence, headache	Convulsion, balance disorder, dizziness, lethargy, tremor	Amnesia, memory impairment, coordination abnormal/ataxia, paraesthesia, disturbance in attention	Choreoathetosis, dyskinesia, hyperkinesia
<u>Eye disorders</u>			Diplopia, vision blurred	
<u>Ear and labyrinth disorders</u>		Vertigo		
<u>Respiratory, thoracic and mediastinal disorders</u>		Cough		
<u>Gastrointestinal disorders</u>		Abdominal pain, diarrhoea, dyspepsia, vomiting, nausea		Pancreatitis
<u>Hepatobiliary disorders</u>			Liver function test abnormal	Hepatic failure, hepatitis
<u>Renal and Urinary Disorders</u>				Acute Kidney injury
<u>Skin and subcutaneous tissue disorders</u>		Rash	Alopecia, eczema, pruritus,	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme

<u>MedDRA SOC</u>	<u>Frequency category</u>			
	<u>Very common</u>	<u>Common</u>	<u>Uncommon</u>	<u>Rare</u>
<u>Musculoskeletal and connective tissue disorders</u>			Muscular weakness, myalgia	Rhabdomyolysis and blood creatine phosphokinase increased*
<u>General disorders and administration site conditions</u>		Asthenia/fatigue		
<u>Injury, poisoning and procedural complications</u>			Injury	

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

Cases of encephalopathy have been rarely observed after levetiracetam administration. These undesirable effects generally occurred at the beginning of the treatment (few days to a few months) and were reversible after treatment discontinuation.

#### Description of selected adverse reactions

The risk of anorexia is higher when levetiracetam is coadministered with topiramate. In several cases of alopecia, recovery was observed when levetiracetam was discontinued. Bone marrow suppression was identified in some of the cases of pancytopenia.

#### Paediatric population

In patients aged 1 month to less than 4 years, a total of 190 patients have been treated with levetiracetam in placebo-controlled and open label extension studies. Sixty of these patients were treated with levetiracetam in placebo-controlled studies. In patients aged 4-16 years, a total of 645 patients have been treated with levetiracetam in placebo-controlled and open label extension studies. 233 of these patients were treated with levetiracetam in placebo-controlled studies. In both these paediatric age ranges, these data are supplemented with the post-marketing experience of the use of levetiracetam.

In addition, 101 infants aged less than 12 months have been exposed in a post authorization safety study. No new safety concerns for levetiracetam were identified for infants less than 12 months of age with epilepsy.

The adverse reaction profile of levetiracetam is generally similar across age groups and across the approved epilepsy indications. Safety results in paediatric patients in placebo-controlled clinical studies were consistent with the safety profile of levetiracetam in adults except for behavioural and psychiatric adverse reactions which were more common in children than in adults. In children and adolescents aged 4 to 16 years, vomiting (very common, 11.2%), agitation (common, 3.4%), mood swings (common, 2.1%), affect lability (common, 1.7%), aggression (common, 8.2%), abnormal behaviour (common, 5.6%), and lethargy (common, 3.9%) were reported more frequently than in other age ranges or in the overall safety profile. In infants and children aged 1 month to less than 4 years, irritability (very common, 11.7%) and coordination abnormal (common, 3.3%) were reported more frequently than in other age groups or in the overall safety profile.

A double-blind, placebo-controlled paediatric safety study with a non-inferiority design has assessed the cognitive and neuropsychological effects of levetiracetam in children 4 to 16 years of age with partial onset seizures. It was concluded that Keppra was not different (non inferior) from placebo with regard to the change from baseline of the Leiter-R Attention and Memory, Memory Screen Composite

score in the per-protocol population. Results related to behavioural and emotional functioning indicated a worsening in levetiracetam-treated patients on aggressive behaviour as measured in a standardised and systematic way using a validated instrument (CBCL – Achenbach Child Behavior Checklist). However subjects, who took levetiracetam in the long-term open label follow-up study, did not experience a worsening, on average, in their behavioural and emotional functioning; in particular measures of aggressive behaviour were not worse than baseline.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## **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, other antiepileptics, ATC code: N03AX14.

The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of  $\alpha$ -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. *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  $\text{Ca}^{2+}$  levels by partial inhibition of N-type  $\text{Ca}^{2+}$  currents and by reducing the release of  $\text{Ca}^{2+}$  from intraneuronal stores. In addition, it partially reverses the reductions in GABA- and glycine-gated currents induced by zinc and  $\beta$ -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 efficacy and safety

*Adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents 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.

### Paediatric population

In paediatric 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.

35 infants aged less than 1 year with partial onset seizures have been exposed in placebo-control clinical studies of which only 13 were aged < 6 months.

*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 twice daily 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 (C<sub>max</sub>) 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 P<sub>450</sub> 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<sub>450</sub> 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).

### 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).

## Paediatric population

### *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.

### **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential.

Adverse effects not observed in clinical studies but seen in the rat and to a lesser extent in the mouse at exposure levels similar to human exposure levels and with possible relevance for clinical use were liver changes, indicating an adaptive response such as increased weight and centrilobular hypertrophy, fatty infiltration and increased liver enzymes in plasma.

No adverse reactions on male or female fertility or reproduction performance were observed in rats at doses up to 1800 mg/kg/day (x 6 the MRHD on a mg/m<sup>2</sup> or exposure basis) in parents and F1 generation.

Two embryo-foetal development (EFD) studies were performed in rats at 400, 1200 and 3600 mg/kg/day. At 3600 mg/kg/day, in only one of the 2 EFD studies, there was a slight decrease in foetal weight associated with a marginal increase in skeletal variations/minor anomalies. There was no effect on embryomortality and no increased incidence of malformations. The NOAEL (No Observed Adverse Effect Level) was 3600 mg/kg/day for pregnant female rats (x 12 the MRHD on a mg/m<sup>2</sup> basis) and 1200 mg/kg/day for fetuses.

Four embryo-foetal development studies were performed in rabbits covering doses of 200, 600, 800, 1200 and 1800 mg/kg/day. The dose level of 1800 mg/kg/day induced a marked maternal toxicity and a decrease in foetal weight associated with increased incidence of fetuses with cardiovascular/skeletal anomalies. The NOAEL was <200 mg/kg/day for the dams and 200 mg/kg/day for the fetuses (equal to the MRHD on a mg/m<sup>2</sup> basis).

A peri- and post-natal development study was performed in rats with levetiracetam doses of 70, 350 and 1800 mg/kg/day. The NOAEL was ≥ 1800 mg/kg/day for the F0 females, and for the survival, growth and development of the F1 offspring up to weaning (x 6 the MRHD on a mg/m<sup>2</sup> basis).

Neonatal and juvenile animal studies in rats and dogs demonstrated that there were no adverse effects seen in any of the standard developmental or maturation endpoints at doses up to 1800 mg/kg/day (x 6-17 the MRHD on a mg/m<sup>2</sup> basis)

## **6. PHARMACEUTICAL PARTICULARS**

## 6.1 List of excipients

Sodium acetate  
Glacial acetic acid  
Sodium chloride  
Water for injections

## 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

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

This medicinal product does not require any special storage conditions.  
For storage conditions of the diluted medicinal product, see section 6.3.

## 6.5 Nature and contents of container

5 ml glass vial (type I) closed by a polytetrafluoroethylene grey chlorobutyl rubber stopper or an uncoated grey bromobutyl rubber stopper and sealed with an aluminium/polypropylene flip cap. Each carton contains 10 vials.

## 6.6 Special precautions for disposal and other handling

See Table 1 for the recommended preparation and administration of Keppra concentrate for solution for infusion to achieve a total daily dose of 500 mg, 1,000 mg, 2,000 mg, or 3,000 mg in two divided doses.

Table 1. Preparation and administration of Keppra concentrate for solution for infusion

Dose	Withdrawal Volume	Volume of Diluent	Infusion Time	Frequency of Administration	Total Daily Dose
250 mg	2.5 ml (half 5 ml vial)	100 ml	15 minutes	Twice daily	500 mg/day
500 mg	5 ml (one 5 ml vial)	100 ml	15 minutes	Twice daily	1000 mg/day
1000 mg	10 ml (two 5 ml vials)	100 ml	15 minutes	Twice daily	2000 mg/day
1500 mg	15 ml (three 5 ml vials)	100 ml	15 minutes	Twice daily	3000 mg/day

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

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

Diluents:

- Sodium chloride 9 mg/ml (0.9%) solution for injection
- Lactated Ringer's solution for injection

- Dextrose 50 mg/ml (5%) solution for injection

Medicinal product with particulate matter or discoloration should not be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

#### **7. MARKETING AUTHORISATION HOLDER**

UCB Pharma SA  
Allée de la Recherche 60  
B-1070 Brussels  
Belgium

#### **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/00/146/030  
EU/1/00/146/033

#### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 29 September 2000

Date of latest renewal: 20 August 2015

#### **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

## **ANNEX II**

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

### Name and address of the manufacturers responsible for batch release

#### Film-coated tablets

UCB Pharma SA Chemin du Foriest B-1420 Braine l'Alleud Belgium	or	Aesica Pharmaceuticals S.r.l. Via Praglia, 15 I-10044 Pianezza Italy
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#### Concentrate for solution for infusion

UCB Pharma SA Chemin du Foriest B-1420 Braine l'Alleud Belgium	or	Aesica Pharmaceuticals S.r.l. Via Praglia, 15 I-10044 Pianezza Italy
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#### 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 OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**



## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Box of 20, 30, 50, 60, 100, 100 (100 x 1)**

**1. NAME OF THE MEDICINAL PRODUCT**

Kepra 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  
100 x 1 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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

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

**8. EXPIRY DATE**

EXP

**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**

UCB Pharma SA  
Allée de la Recherche 60  
B-1070 Brussels  
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 (2 packs of 100)*  
EU/1/00/146/034 *100 x 1 tablets*

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Kepra 250 mg  
Justification for not including Braille accepted *100 x 1 tablets*

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Box of 200 (2 x 100) containing blue box**

**1. NAME OF THE MEDICINAL PRODUCT**

Kepra 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**

Multipack: 200 (2 packs of 100) 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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

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

**8. EXPIRY DATE**

EXP

**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**

UCB Pharma SA  
Allée de la Recherche 60  
B-1070 Brussels  
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 (2 packs of 100)*  
EU/1/00/146/034 *100 x 1 tablets*

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Kepra 250 mg

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Intermediate packaging containing 100 tablets for box of 200 (2 x 100) tablets without blue box**

**1. NAME OF THE MEDICINAL PRODUCT**

Kepra 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**

100 film-coated tablets  
Component of a multipack, can't be sold separately.

**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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

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

**8. EXPIRY DATE**

EXP

**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**

UCB Pharma SA  
Allée de la Recherche 60  
B-1070 Brussels  
BELGIUM

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

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Kepra 250 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**Aluminium/PVC blister**

**1. NAME OF THE MEDICINAL PRODUCT**

Kepra 250 mg film-coated tablets  
Levetiracetam

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

UCB logo.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**



**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Box of 10, 20, 30, 50, 60, 100, 100 (100 x 1), 120**

**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  
100 x 1 film-coated tablets  
120 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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

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

**8. EXPIRY DATE**

EXP

**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**

UCB Pharma SA  
Allée de la Recherche 60  
B-1070 Brussels  
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 (2 packs of 100)*  
EU/1/00/146/035 *100 x 1 tablets*

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Kepra 500 mg  
Justification for not including Braille accepted *100 x 1 tablets*

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Box of 200 (2 x 100) with blue box**

**1. NAME OF THE MEDICINAL PRODUCT**

Kepra 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**

Multipack: 200 (2 packs of 100) 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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

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

**8. EXPIRY DATE**

EXP

**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**

UCB Pharma SA  
Allée de la Recherche 60  
B-1070 Brussels  
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 (2 packs of 100)*  
EU/1/00/146/035 *100 x 1 tablets*

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Kepra 500 mg

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Intermediate packaging containing 100 tablets for box of 200 (2 x 100) tablets without blue box**

**1. NAME OF THE MEDICINAL PRODUCT**

Kepra 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**

100 film-coated tablets  
Component of a multipack, can't be sold separately.

**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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

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

**8. EXPIRY DATE**

EXP

**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**

UCB Pharma SA  
Allée de la Recherche 60  
B-1070 Brussels  
BELGIUM

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

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Kepra 500 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**Aluminium/PVC blister**

**1. NAME OF THE MEDICINAL PRODUCT**

Kepra 500 mg film-coated tablets  
Levetiracetam

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

UCB logo.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Box of 20, 30, 50, 60, 80, 100, 100 (100 x 1)**

**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**

Contains sunset yellow (E 110). See the package 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  
100 x 1 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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

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



**8. EXPIRY DATE**

EXP

**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**

UCB Pharma SA  
Allée de la Recherche 60  
B-1070 Brussels  
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 (2 packs of 100)*  
EU/1/00/146/036 *100 x 1 tablets*

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Kepra 750 mg  
Justification for not including Braille accepted *100 x 1 tablets*

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Box of 200 (2 x 100) with blue box**

**1. NAME OF THE MEDICINAL PRODUCT**

Kepra 750 mg film-coated tablets  
Levetiracetam

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

Each film-coated tablet contains 750 mg levetiracetam.

**3. LIST OF EXCIPIENTS**

Contains sunset yellow (E 110). See the package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Multipack: 200 (2 packs of 100) 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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

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

**8. EXPIRY DATE**

EXP

**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**

UCB Pharma SA  
Allée de la Recherche 60  
B-1070 Brussels  
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 (2 packs of 100)*  
EU/1/00/146/036 *100 x 1 tablets*

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Kepra 750 mg

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Intermediate packaging containing 100 tablets for box of 200 (2 x 100) tablets without blue box**

**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**

Contains sunset yellow (E 110). See the package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

100 film-coated tablets  
Component of a multipack, can't be sold separately.

**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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

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

**8. EXPIRY DATE**

EXP

**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**

UCB Pharma SA  
Allée de la Recherche 60  
B-1070 Brussels  
BELGIUM

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

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Kepra 750 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**Aluminium/PVC blister**

**1. NAME OF THE MEDICINAL PRODUCT**

Kepra 750 mg film-coated tablets  
Levetiracetam

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

UCB logo.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Box of 10, 20, 30, 50, 60, 100, 100 (100 x 1)**

**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  
100 x 1 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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

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

**8. EXPIRY DATE**

EXP

**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**

UCB Pharma SA  
Allée de la Recherche 60  
B-1070 Brussels  
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 (2 packs of 100)*  
EU/1/00/146/037 *100 x 1 tablets*

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Kepra 1000 mg  
Justification for not including Braille accepted *100 x 1 tablets*



**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Box of 200 (2 x 100) with blue box**

**1. NAME OF THE MEDICINAL PRODUCT**

Kepra 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**

Multipack: 200 (2 packs of 100) 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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

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

**8. EXPIRY DATE**

EXP

**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**

UCB Pharma SA  
Allée de la Recherche 60  
B-1070 Brussels  
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 (2 packs of 100)*  
EU/1/00/146/037 *100 x 1 tablets*

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Kepra 1000 mg

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Intermediate packaging containing 100 tablets for box of 200 (2 x 100) tablets without blue box**

**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**

100 film-coated tablets  
Component of a multipack, can't be sold separately.

**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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

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

**8. EXPIRY DATE**

EXP

**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**

UCB Pharma SA  
Allée de la Recherche 60  
B-1070 Brussels  
BELGIUM

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

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Kepra 1000 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**Aluminium/PVC blister**

**1. NAME OF THE MEDICINAL PRODUCT**

Kepra 1000 mg film-coated tablets  
Levetiracetam

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

UCB logo.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

Bottle of 300 ml

**1. NAME OF THE MEDICINAL PRODUCT**

Kepra 100 mg/ml oral solution  
Levetiracetam  
For adults and children aged 4 years and older.

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

Each ml contains 100 mg levetiracetam.

**3. LIST OF EXCIPIENTS**

Contains E216, E218 and maltitol liquid.

**4. PHARMACEUTICAL FORM AND CONTENTS**

300 ml oral solution

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

Read the package leaflet before use.  
Oral use.  
Only use the 10 ml syringe included in the package.

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

Keep out of the sight and reach of children.

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

**8. EXPIRY DATE**

EXP  
Do not use after 7 months of first opening the bottle.  
Date of opening *only for the outer carton*

**9. SPECIAL STORAGE CONDITIONS**

Store in the original bottle in order to protect from light.

**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**

UCB Pharma SA  
Allée de la Recherche 60  
B-1070 Brussels  
BELGIUM

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

EU/1/00/146/027

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Keppra 100 mg/ml *only for the outer carton*

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

Bottle of 150 ml

**1. NAME OF THE MEDICINAL PRODUCT**

Kepra 100 mg/ml oral solution  
Levetiracetam  
For children aged 6 months to less than 4 years.

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

Each ml contains 100 mg levetiracetam.

**3. LIST OF EXCIPIENTS**

Contains E216, E218 and maltitol liquid.

**4. PHARMACEUTICAL FORM AND CONTENTS**

150 ml oral solution

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

Read the package leaflet before use.  
Oral use.  
Only use the 3 ml syringe included in the package.

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

Keep out of the sight and reach of children.

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

**8. EXPIRY DATE**

EXP  
Do not use after 7 months of first opening the bottle.  
Date of opening *only for the outer carton*



**9. SPECIAL STORAGE CONDITIONS**

Store in the original bottle in order to protect from light.

**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**

UCB Pharma SA  
Allée de la Recherche 60  
B-1070 Brussels  
BELGIUM

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

EU/1/00/146/031

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Keppra 100 mg/ml *only for the outer carton*

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

Bottle of 150 ml

**1. NAME OF THE MEDICINAL PRODUCT**

Kepra 100 mg/ml oral solution  
Levetiracetam  
For children aged 1 month to less than 6 months.

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

Each ml contains 100 mg levetiracetam.

**3. LIST OF EXCIPIENTS**

Contains E216, E218 and maltitol liquid.

**4. PHARMACEUTICAL FORM AND CONTENTS**

150 ml oral solution

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

Read the package leaflet before use.  
Oral use.  
Only use the 1 ml syringe included in the package.

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

Keep out of the sight and reach of children.

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

**8. EXPIRY DATE**

EXP  
Do not use after 7 months of first opening the bottle.  
Date of opening *only for the outer carton*

**9. SPECIAL STORAGE CONDITIONS**

Store in the original bottle in order to protect from light.

**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**

UCB Pharma SA  
Allée de la Recherche 60  
B-1070 Brussels  
BELGIUM

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

EU/1/00/146/032

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Keppra 100 mg/ml *only for the outer carton*

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Box of 10 vials**

**1. NAME OF THE MEDICINAL PRODUCT**

Kepra 100 mg/ml concentrate for solution for infusion  
Levetiracetam

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

One vial contains 500 mg/5 ml levetiracetam.  
Each ml contains 100 mg levetiracetam.

**3. LIST OF EXCIPIENTS**

Other ingredients include sodium acetate, glacial acetic acid, sodium chloride, water for injections.  
See the package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

500 mg/5 ml  
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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

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

**8. EXPIRY DATE**

EXP  
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**

UCB Pharma SA  
Allée de la Recherche 60  
B-1070 Brussels  
BELGIUM

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

EU/1/00/146/030 (polytetrafluoroethylene *-faced stopper*)  
EU/1/00/146/033 (*Uncoated stopper*)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

Vial of 5 ml

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

Kepra 100 mg/ml sterile concentrate  
Levetiracetam  
IV

**2. METHOD OF ADMINISTRATION**

Read the package leaflet before use.

**3. EXPIRY DATE**

EXP  
Use immediately after dilution.

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

500 mg/5 ml

**6. OTHER**

**B. PACKAGE LEAFLET**

## Package Leaflet: Information for the patient

**Keppra 250 mg film-coated tablets**  
**Keppra 500 mg film-coated tablets**  
**Keppra 750 mg film-coated tablets**  
**Keppra 1000 mg film-coated tablets**  
Levetiracetam

**Read all of this leaflet carefully before you or your child start taking this medicine because it contains important information for you.**

- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

### What is in this leaflet

1. What Keppra is and what it is used for
2. What you need to know before you take Keppra
3. How to take Keppra
4. Possible side effects
5. How to store Keppra
6. Contents of the pack and other information

### 1. What Keppra is and what it is used for

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

Keppra is used:

- on its own in adults and adolescents from 16 years of age with newly diagnosed epilepsy, to treat a certain form of epilepsy. Epilepsy is a condition where the patients have repeated fits (seizures). Levetiracetam is used for the epilepsy form in which the fits initially affect only one side of the brain, but could thereafter extend to larger areas on both sides of the brain (partial onset seizure with or without secondary generalisation). Levetiracetam has been given to you by your doctor to reduce the number of fits.
- as an add-on to other antiepileptic medicines to treat:
  - partial onset seizures with or without generalisation in adults, adolescents, children and infants from one month of age;
  - myoclonic seizures (short, shock-like jerks of a muscle or group of muscles) in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy;
  - primary generalised tonic-clonic seizures (major fits, including loss of consciousness) in adults and adolescents from 12 years of age with idiopathic generalised epilepsy (the type of epilepsy that is thought to have a genetic cause).

### 2. What you need to know before you take Keppra

#### Do not take Keppra

- If you are allergic to levetiracetam, pyrrolidone derivatives or any of the other ingredients of this medicine (listed in Section 6).

#### Warnings and precautions

Talk to your doctor before taking Keppra



- If you suffer from kidney problems, follow your doctor's instructions. He/she may decide if your dose should be adjusted.
- If you notice any slow down in the growth or unexpected puberty development of your child, please contact your doctor.
- A small number of people being treated with anti-epileptics such as Keppra have had thoughts of harming or killing themselves. If you have any symptoms of depression and/or suicidal ideation, please contact your doctor.

### **Children and adolescents**

- Keppra is not indicated in children and adolescents below 16 years on its own (monotherapy).

### **Other medicines and Keppra**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Do not take macrogol (a drug used as laxative) for one hour before and one hour after taking levetiracetam as this may result in a loss of its effect.

### **Pregnancy and breast-feeding**

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Keppra should not be used during pregnancy unless clearly necessary. A risk of birth defects for your unborn child cannot be completely excluded. 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 it 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.

### **Keppra 750 mg tablets contain Sunset Yellow FCF (E110).**

Sunset Yellow FCF (E110) colouring agent may cause allergic reactions.

## **3. How to take Keppra**

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Take the number of tablets following your doctor's instructions.

Keppra must be taken twice a day, once in the morning and once in the evening, at about the same time each day.

### ***Monotherapy***

- **Dose in adults and adolescents (from 16 years of age):**  
General dose: between 1000 mg and 3,000 mg each day.  
When you will first start taking Keppra, your doctor will prescribe you a **lower dose** during 2 weeks before giving you the lowest general dose.  
*Example: if your daily dose is 1000 mg, your reduced starting dose is 2 tablets of 250 mg in the morning and 2 tablets of 250 mg in the evening.*

### ***Add-on therapy***

- **Dose 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.  
*Example: if your daily dose is 1,000 mg, you might take 2 tablets of 250 mg in the morning and 2 tablets of 250 mg in the evening.*
- **Dose in infants (1 month to 23 months), children (2 to 11 years) and adolescents (12 to 17 years) weighing less than 50 kg:**  
Your doctor will prescribe the most appropriate pharmaceutical form of Keppra according to the age, weight and dose.

Keppra 100 mg/ml oral solution is a formulation more appropriate to infants and children under the age of 6 years and to children and adolescent (from 6 to 17 years) weighing less than 50kg and when tablets don't allow accurate dosage.

#### Method of administration

Swallow Keppra tablets with a sufficient quantity of liquid (*e.g.* a glass of water). You may take Keppra with or without food.

#### 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.

#### **If you take more Keppra than you should**

The possible side effects of an overdose of Keppra are sleepiness, agitation, aggression, decrease of alertness, inhibition of breathing and coma.

Contact your doctor if you took more tablets than you should. Your doctor will establish the best possible treatment of overdose.

#### **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, Keppra should be discontinued gradually to avoid an increase of seizures.

Should your doctor decide to stop your Keppra treatment, he/she will instruct you about the gradual withdrawal of Keppra.

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

## **4. Possible side effects**

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

#### **Tell your doctor immediately, or go to your nearest emergency department, if you experience:**

- weakness, feel light-headed or dizzy or have difficulty breathing, as these may be signs of a serious allergic (anaphylactic) reaction
- swelling of the face, lips, tongue and throat (Quincke's oedema)
- flu-like symptoms and a rash on the face followed by an extended rash with a high temperature, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia) and enlarged lymph nodes (Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS])

- symptoms such as low urine volume, tiredness, nausea, vomiting, confusion and swelling in the legs, ankles or feet, as this may be a sign of sudden decrease of kidney function
- a skin rash which may form blisters and look like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) (*erythema multiforme*)
- a widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (*Stevens-Johnson syndrome*)
- a more severe form of rash causing skin peeling in more than 30% of the body surface (*toxic epidermal necrolysis*)
- signs of serious mental changes or if someone around you notices signs of confusion, somnolence (sleepiness), amnesia (loss of memory), memory impairment (forgetfulness), abnormal behaviour or other neurological signs including involuntary or uncontrolled movements. These could be symptoms of an encephalopathy.

The most frequently reported side effects are nasopharyngitis, somnolence (sleepiness), headache, fatigue and dizziness. At the beginning of the treatment or at dose increase side effects like sleepiness, tiredness and dizziness may be more common. These effects should however decrease over time.

**Very common:** may affect more than 1 user in 10 people

- nasopharyngitis;
- somnolence (sleepiness), headache.

**Common:** may affect 1 to 10 users in 100 people

- anorexia (loss of appetite);
- depression, hostility or aggression, anxiety, insomnia, nervousness or irritability;
- convulsion, balance disorder (equilibrium disorder), dizziness (sensation of unsteadiness), lethargy (lack of energy and enthusiasm), tremor (involuntary trembling);
- vertigo (sensation of rotation);
- cough;
- abdominal pain, diarrhoea, dyspepsia (indigestion), vomiting, nausea;
- rash;
- asthenia/fatigue (tiredness).

**Uncommon:** may affect 1 to 10 users in 1000 people

- decreased number of blood platelets, decreased number of white blood cells;
- weight decrease, weight increase;
- suicide attempt and suicidal ideation, mental disorder, abnormal behaviour, hallucination, anger, confusion, panic attack, emotional instability/mood swings, agitation;
- amnesia (loss of memory), memory impairment (forgetfulness), abnormal coordination/ataxia (impaired coordinated movements), paraesthesia (tingling), disturbance in attention (loss of concentration);
- diplopia (double vision), vision blurred;
- elevated/abnormal values in a liver function test;
- hair loss, eczema, pruritus;
- muscle weakness, myalgia (muscle pain);
- injury.

**Rare:** may affect 1 to 10 users in 10,000 people

- infection;
- decreased number of all blood cell types;
- severe allergic reactions (DRESS, anaphylactic reaction [severe and important allergic reaction], Quincke's oedema [swelling of the face, lips, tongue and throat]);
- decreased blood sodium concentration;
- suicide, personality disorders (behavioural problems), thinking abnormal (slow thinking, unable to concentrate);

- uncontrollable muscle spasms affecting the head, torso and limbs, difficulty in controlling movements, hyperkinesia (hyperactivity);
- pancreatitis;
- liver failure, hepatitis;
- sudden decrease in kidney function
- skin rash, which may form blisters and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) (*erythema multiforme*), a widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (*Stevens–Johnson syndrome*), and a more severe form causing skin peeling in more than 30% of the body surface (*toxic epidermal necrolysis*).
- rhabdomyolysis (breakdown of muscle tissue) and associated blood creatine phosphokinase increase. Prevalence is significantly higher in Japanese patients when compared to non-Japanese patients.

### Reporting of side effects

If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Keppra

Keep this medicine out of the sight and reach of children.

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

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

### What Keppra contains

The active substance is called levetiracetam.

One tablet of Keppra 250 mg contains 250 mg of levetiracetam.

One tablet of Keppra 500 mg contains 500 mg of levetiracetam.

One tablet of Keppra 750 mg contains 750 mg of levetiracetam.

One tablet of Keppra 1,000 mg contains 1,000 mg of levetiracetam.

The other ingredients are:

*Tablet core:* croscarmellose sodium, macrogol 6000, silica colloidal anhydrous, magnesium stearate.

*Film-coating:* Polyvinyl alcohol-part. hydrolyzed, titanium dioxide (E171), macrogol 3350, talc, colourants\*.

\* The colourants are:

250 mg tablet: indigo carmine aluminium lake (E132)

500 mg tablet: iron oxide yellow (E172)

750 mg tablet: sunset yellow FCF (E110), iron oxide red (E172)

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

Keppra 250 mg film-coated tablets are blue, 13 mm oblong, scored and debossed with the code “ucb” and “250” on one side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Keppra 500 mg film-coated tablets are yellow, 16 mm oblong, scored and debossed with the code “ucb” and “500” on one side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Keppra 750 mg film-coated tablets are orange, 18 mm oblong, scored and debossed with the code “ucb” and “750” on one side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Keppra 1000 mg film-coated tablets are white, 19 mm oblong, scored and debossed with the code “ucb” and “1000” on one side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Keppra tablets are packaged in blister packs supplied in cardboard boxes containing:

- 250 mg: 20, 30, 50, 60, 100 x 1, 100 film-coated tablets and multipacks containing 200 (2 packs of 100) film-coated tablets
- 500 mg: 10, 20, 30, 50, 60, 100 x 1, 100, 120 film-coated tablets and multipacks containing 200 (2 packs of 100) film-coated tablets
- 750 mg: 20, 30, 50, 60, 80, 100 x 1, 100 film-coated tablets and multipacks containing 200 (2 packs of 100) film-coated tablets
- 1000 mg: 10, 20, 30, 50, 60, 100 x 1, 100 film-coated tablets and multipacks containing 200 (2 packs of 100) film-coated tablets

The 100 x 1 tablet packs are available in aluminium/PVC perforated unit dose blisters. All other packs are available in standard aluminium/PVC blisters.

Not all pack sizes may be marketed.

#### **Marketing Authorisation Holder**

UCB Pharma SA, Allée de la Recherche 60, B-1070 Brussels, Belgium.

#### **Manufacturer**

UCB Pharma SA, Chemin du Foriest, B-1420 Braine-l'Alleud, Belgium.

or Aesica Pharmaceuticals S.r.l., Via Praglia 15, I-10044 Pianezza, Italy

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

#### **België/Belgique/Belgien**

UCB Pharma SA/NV

Tel/Tél: + 32 / (0)2 559 92 00

#### **Lietuva**

UCB Pharma Oy Finland

Tel: +358 9 2514 4221 (Suomija)

#### **България**

Ю СИ БИ България ЕООД

Тел.: + 359 (0) 2 962 30 49

#### **Luxembourg/Luxemburg**

UCB Pharma SA/NV

Tél/Tel: + 32 / (0)2 559 92 00

**Česká republika**

UCB s.r.o.  
Tel: + 420 221 773 411

**Danmark**

UCB Nordic A/S  
Tlf: + 45 / 32 46 24 00

**Deutschland**

UCB Pharma GmbH  
Tel: + 49 / (0) 2173 48 4848

**Eesti**

UCB Pharma Oy Finland  
Tel: +358 9 2514 4221 (Soome)

**Ελλάδα**

UCB A.E.  
Τηλ: + 30 / 2109974000

**España**

UCB Pharma, S.A.  
Tel: + 34 / 91 570 34 44

**France**

UCB Pharma S.A.  
Tél: + 33 / (0)1 47 29 44 35

**Hrvatska**

Medis Adria d.o.o.  
Tel: +385 (0) 1 230 34 46

**Ireland**

UCB (Pharma) Ireland Ltd.  
Tel: + 353 / (0)1-46 37 395

**Ísland**

Vistor hf.  
Tel: + 354 535 7000

**Italia**

UCB Pharma S.p.A.  
Tel: + 39 / 02 300 791

**Κύπρος**

Lifepharm (Z.A.M.) Ltd  
Τηλ: + 357 22 34 74 40

**Latvija**

UCB Pharma Oy Finland  
Tel: +358 9 2514 4221 (Somija)

**Magyarország**

UCB Magyarország Kft.  
Tel.: + 36-(1) 391 0060

**Malta**

Pharmasud Ltd.  
Tel: + 356 / 21 37 64 36

**Nederland**

UCB Pharma B.V.  
Tel.: + 31 / (0)76-573 11 40

**Norge**

UCB Nordic A/S  
Tlf: + 45 / 32 46 24 00

**Österreich**

UCB Pharma GmbH  
Tel: + 43 (0)1 291 80 00

**Polska**

UCB Pharma Sp. z o.o.  
Tel: + 48 22 696 99 20

**Portugal**

UCB Pharma (Produtos Farmacêuticos), Lda  
Tel: + 351 / 21 302 5300

**România**

UCB Pharma Romania S.R.L.  
Tel: + 40 21 300 29 04

**Slovenija**

Medis, d.o.o.  
Tel: + 386 1 589 69 00

**Slovenská republika**

UCB s.r.o., organizačná zložka  
Tel: + 421 (0) 2 5920 2020

**Suomi/Finland**

UCB Pharma Oy Finland  
Puh/Tel: +358 9 2514 4221

**Sverige**

UCB Nordic A/S  
Tel: + 46 / (0) 40 29 49 00

**United Kingdom**

UCB Pharma Ltd.  
Tel : + 44 / (0)1753 534 655

**This leaflet was last revised in {month/YYYY}**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>

## Package Leaflet: Information for the patient

### Keppra 100 mg/ml oral solution

Levetiracetam

**Read all of this leaflet carefully before you or your child start taking this medicine because it contains important information for you.**

- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet:**

1. What Keppra is and what it is used for
2. What you need to know before you take Keppra
3. How to take Keppra
4. Possible side effects
5. How to store Keppra
6. Contents of the pack and other information

### **1. What Keppra is and what it is used for**

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

Keppra is used:

- on its own in adults and adolescents from 16 years of age with newly diagnosed epilepsy, to treat a certain form of epilepsy. Epilepsy is a condition where the patients have repeated fits (seizures). Levetiracetam is used for the epilepsy form in which the fits initially affect only one side of the brain, but could thereafter extend to larger areas on both sides of the brain (partial onset seizure with or without secondary generalisation). Levetiracetam has been given to you by your doctor to reduce the number of fits.
- as an add-on to other antiepileptic medicines to treat:
  - partial onset seizures with or without generalisation in adults, adolescents, children and infants from one month of age
  - myoclonic seizures (short, shock-like jerks of a muscle or group of muscles) in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy
  - primary generalised tonic-clonic seizures (major fits, including loss of consciousness) in adults and adolescents from 12 years of age with idiopathic generalised epilepsy (the type of epilepsy that is thought to have a genetic cause).

### **2. What you need to know before you take Keppra**

#### **Do not take Keppra**

- If you are allergic to levetiracetam, pyrrolidone derivatives or any of the other ingredients of this medicine (listed in Section 6).

#### **Warnings and precautions**

Talk to your doctor before taking Keppra

- If you suffer from kidney problems, follow your doctor's instructions. He/she may decide if your dose should be adjusted.
- If you notice any slow down in the growth or unexpected puberty development of your child, please contact your doctor.



- A small number of people being treated with anti-epileptics such as Keppra have had thoughts of harming or killing themselves. If you have any symptoms of depression and/or suicidal ideation, please contact your doctor.

### **Children and adolescents**

- Keppra is not indicated in children and adolescents below 16 years on it's own (monotherapy)

### **Other medicines and Keppra**

Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicines.

Do not take macrogol (a drug used as laxative) for one hour before and one hour after taking levetiracetam as this may result in a reduction of its effect.

### **Pregnancy and breast-feeding**

If you are pregnant or breastfeeding, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before taking this medicine..

Keppra should not be used during pregnancy unless clearly necessary. A risk of birth defects for your unborn child cannot be completely excluded. 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 it 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.

### **Keppra contains methyl parahydroxybenzoate, propyl parahydroxybenzoate and maltitol**

Keppra oral solution includes methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) which may cause allergic reactions (possibly delayed).

Keppra oral solution also contains maltitol. 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**

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Keppra must be taken twice a day, once in the morning and once in the evening, at about the same time each day.

Take the oral solution following your doctor's instructions.

### ***Monotherapy***

#### **Dose in adults and adolescents (from 16 years of age):**

Measure the appropriate dosage using the 10 ml syringe included in the package for patients 4 years and above.

General dose: Keppra is taken twice daily, in two equally divided doses, each individual dose being measured between 5 ml (500mg) and 15 ml (1500mg).

When you will first start taking Keppra, your doctor will prescribe you a **lower dose** during 2 weeks before giving you the lowest general dose.

### ***Add-on therapy***

#### **Dose in adults and adolescents (12 to 17 years):**

Measure the appropriate dosage using the 10 ml syringe included in the package for patients of 4 years and above.

**General dose:** Keppra is taken twice daily, in two equally divided doses, each individual dose being measured between 5 ml (500mg) and 15 ml (1500mg).

**Dose in children 6 months and older :**

Your doctor will prescribe the most appropriate pharmaceutical form of Keppra according to the age, weight and dose.

**For children 6 months to 4 years,** measure the appropriate dosage using the **3 ml** syringe included in the package.

**For children above 4 years,** measure the appropriate dosage using the **10 ml** syringe included in the package.

**General dose:** Keppra is taken twice daily, in two equally divided doses, each individual dose being measured between 0.1 ml (10mg) and 0.3 ml (30mg), per kg bodyweight of the child. (see table below for dose examples).

**Dose in children 6 months and older:**

Weight	Starting dose: 0.1 ml/kg twice daily	Maximum dose: 0.3 ml/kg twice daily
6 kg	0.6 ml twice daily	1.8 ml twice daily
8 kg	0.8 ml twice daily	2.4 ml twice daily
10 kg	1 ml twice daily	3 ml twice daily
15 kg	1.5 ml twice daily	4.5 ml twice daily
20 kg	2 ml twice daily	6 ml twice daily
25 kg	2.5 ml twice daily	7.5 ml twice daily
From 50 kg	5 ml twice daily	15 ml twice daily

**Dose in infants (1 month to less than 6 months):**

**For infants 1 month to less than 6 months,** measure the appropriate dosage using the **1 ml** syringe included in the package.

**General dose:** Keppra is taken twice daily, in two equally divided doses, each individual dose being measured between 0.07 ml (7mg) and 0.21 ml (21mg), per kg bodyweight of the infant. (see table below for dose examples).

**Dose in infants (1 month to less than 6 months):**

Weight	Starting dose: 0.07 ml/kg twice daily	Maximum dose: 0.21 ml/kg twice daily
4 kg	0.3 ml twice daily	0.85 ml twice daily
5 kg	0.35 ml twice daily	1.05 ml twice daily
6 kg	0.45 ml twice daily	1.25 ml twice daily
7 kg	0.5 ml twice daily	1.5 ml twice daily

**Method of administration:**

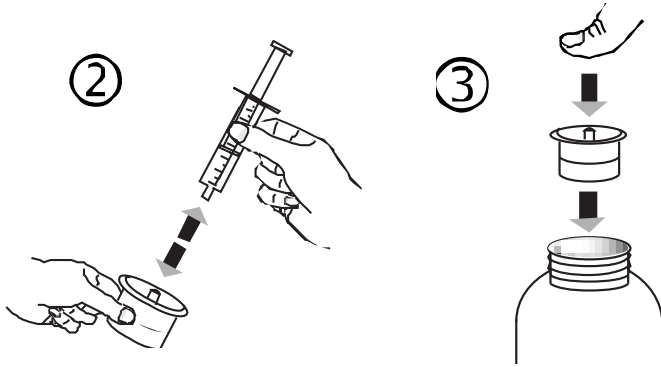
After measuring the correct dosage with an appropriate syringe, Keppra oral solution may be diluted in a glass of water or baby's bottle. You may take Keppra with or without food.

Instructions for use:

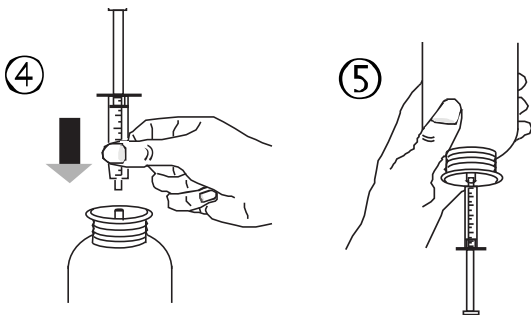
- Open the bottle: press the cap and turn it anticlockwise (figure 1)



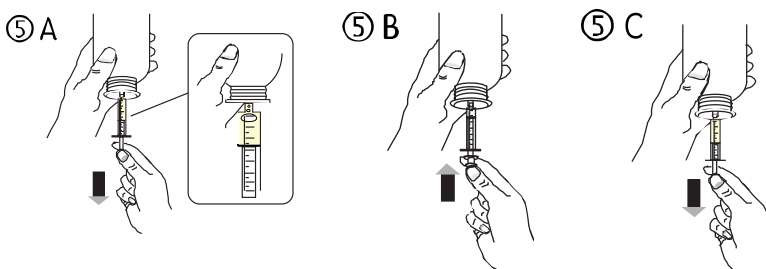
- Separate the adaptor from the syringe (figure 2). Insert the adaptor into the bottle neck (figure 3). Ensure it is well fixed.



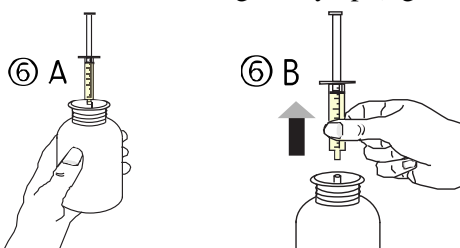
- Take the syringe and put it in the adaptor opening (figure 4). Turn the bottle upside down (figure 5).



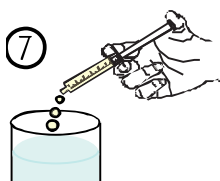
- Fill the syringe with a small amount of solution by pulling the piston down (figure 5A), then push the piston upward in order to remove any possible bubble (figure 5B). Pull the piston down to the graduation mark corresponding to the quantity in milliliters (ml) prescribed by your doctor (figure 5C).



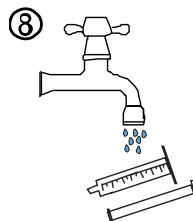
- Turn the bottle the right way up (figure 6A). Remove the syringe from the adaptor (figure 6B).



- Empty the contents of the syringe in a glass of water or baby's bottle by pushing the piston to the bottom of the syringe (figure 7).



- Drink the whole contents of the glass/baby's bottle.
- Close the bottle with the plastic screw cap.
- Wash the syringe with water only (figure 8).



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.

### **If you take more Keppra than you should**

The possible side effects of an overdose of Keppra are sleepiness, agitation, aggression, decrease of alertness, inhibition of breathing and coma.

Contact your doctor if you took more Keppra than you should. Your doctor will establish the best possible treatment of overdose.

### **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, Keppra should be discontinued gradually to avoid an increase of seizures.

Should your doctor decide to stop your Keppra treatment, he/she will instruct you about the gradual withdrawal of Keppra.

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

## **4. Possible side effects**

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

**Tell your doctor immediately, or go to your nearest emergency department, if you experience:**

- weakness, feel light-headed or dizzy or have difficulty breathing, as these may be signs of a serious allergic (anaphylactic) reaction
- swelling of the face, lips, tongue and throat (Quincke's oedema)
- flu-like symptoms and a rash on the face followed by an extended rash with a high temperature, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia) and enlarged lymph nodes (Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS]),.
- symptoms such as low urine volume, tiredness, nausea, vomiting, confusion and swelling in the legs, ankles or feet, as this may be a sign of sudden decrease of kidney function
- a skin rash which may form blisters and look like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) (*erythema multiforme*)
- a widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (*Stevens-Johnson syndrome*)

- a more severe form of rash causing skin peeling in more than 30% of the body surface (*toxic epidermal necrolysis*)
- signs of serious mental changes or if someone around you notices signs of confusion, somnolence (sleepiness), amnesia (loss of memory), memory impairment (forgetfulness), abnormal behaviour or other neurological signs including involuntary or uncontrolled movements. These could be symptoms of an encephalopathy.

The most frequently reported adverse reactions were nasopharyngitis, somnolence (sleepiness), headache, fatigue and dizziness. At the beginning of the treatment or at dose increase side effects like sleepiness, tiredness and dizziness may be more common. These effects should however decrease over time.

**Very common:** may affect more than 1 user in 10 people

- nasopharyngitis;
- somnolence (sleepiness), headache.

**Common:** may affect 1 to 10 users in 100 people

- anorexia (loss of appetite);
- depression, hostility or aggression, anxiety, insomnia, nervousness or irritability;
- convulsion, balance disorder (equilibrium disorder), dizziness (sensation of unsteadiness), lethargy (lack of energy and enthusiasm), tremor (involuntary trembling);
- vertigo (sensation of rotation);
- cough;
- abdominal pain, diarrhoea, dyspepsia (indigestion), vomiting, nausea;
- rash;
- asthenia/fatigue (tiredness).

**Uncommon:** may affect 1 to 10 users in 1000 people

- decreased number of blood platelets, decreased number of white blood cells;
- weight decrease, weight increase;
- suicide attempt and suicidal ideation, mental disorder, abnormal behaviour, hallucination, anger, confusion, panic attack, emotional instability/mood swings, agitation;
- amnesia (loss of memory), memory impairment (forgetfulness), abnormal coordination/ataxia (impaired coordinated movements), paraesthesia (tingling), disturbance in attention (loss of concentration);
- diplopia (double vision), vision blurred;
- elevated/abnormal values in a liver function test;
- hair loss, eczema, pruritus;
- muscle weakness, myalgia (muscle pain);
- injury.

**Rare:** may affect 1 to 10 users in 10,000 people

- infection;
- decreased number of all blood cell types;
- severe allergic reactions (DRESS, anaphylactic reaction [severe and important allergic reaction], Quincke's oedema [swelling of the face, lips, tongue and throat]);
- decreased blood sodium concentration;
- suicide, personality disorders (behavioural problems), thinking abnormal (slow thinking, unable to concentrate);
- uncontrollable muscle spasms affecting the head, torso and limbs, difficulty in controlling movements, hyperkinesia (hyperactivity);
- pancreatitis;
- liver failure, hepatitis;
- sudden decrease in kidney function
- skin rash, which may form blisters and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) (*erythema multiforme*), a widespread rash

with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (*Stevens-Johnson syndrome*), and a more severe form causing skin peeling in more than 30% of the body surface (*toxic epidermal necrolysis*).

- rhabdomyolysis (breakdown of muscle tissue) and associated blood creatine phosphokinase increase. Prevalence is significantly higher in Japanese patients when compared to non-Japanese patients.

### **Reporting of side effects**

If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store Keppra**

Keep this medicine out of the sight and reach of children.

Do not use this medicine 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 7 months of first opening the bottle.

Store in the original bottle, in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What Keppra contains**

The active substance is called levetiracetam. Each ml contains 100 mg of levetiracetam.

The other ingredients are: sodium citrate, citric acid monohydrate, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), ammonium glycyrrhizate, glycerol (E422), maltitol liquid (E965), acesulfame potassium (E950), grape flavour, purified water.

### **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 (for children aged 4 years and above, adolescents and adults) is packed in a cardboard box containing a 10 ml oral syringe (graduated every 0.25 ml) and an adaptor for the syringe.

The 150 ml glass bottle of Keppra (for infants and young children aged from 6 months to less than 4 years) is packed in a cardboard box containing a 3 ml oral syringe (graduated every 0.1 ml) and an adaptor for the syringe.

The 150 ml glass bottle of Keppra (for infants aged 1 month to less than 6 months) is packed in a cardboard box containing a 1 ml oral syringe (graduated every 0.05 ml) and an adaptor for the syringe.

### **Marketing Authorisation Holder**

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

### **Manufacturer**

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

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

**België/Belgique/Belgien**

UCB Pharma SA/NV

Tel/Tél: + 32 / (0)2 559 92 00

**България**

Ю СИ БИ България ЕООД

Тел.: + 359 (0) 2 962 30 49

**Česká republika**

UCB s.r.o.

Tel: + 420 221 773 411

**Danmark**

UCB Nordic A/S

Tlf: + 45 / 32 46 24 00

**Deutschland**

UCB Pharma GmbH

Tel: + 49 / (0) 2173 48 4848

**Eesti**

UCB Pharma Oy Finland

Tel: +358 9 2514 4221 (Soome)

**Ελλάδα**

UCB A.E.

Τηλ: + 30 / 2109974000

**España**

UCB Pharma, S.A.

Tel: + 34 / 91 570 34 44

**France**

UCB Pharma S.A.

Tél: + 33 / (0)1 47 29 44 35

**Hrvatska**

Medis Adria d.o.o.

Tel: +385 (0) 1 230 34 46

**Ireland**

UCB (Pharma) Ireland Ltd.

Tel: + 353 / (0)1-46 37 395

**Ísland**

Vistor hf.

Tel: + 354 535 7000

**Italia**

UCB Pharma S.p.A.

Tel: + 39 / 02 300 791

**Κύπρος**

Lifepharm (Z.A.M.) Ltd

Τηλ: + 357 22 34 74 40

**Lietuva**

UCB Pharma Oy Finland

Tel: +358 9 2514 4221 (Suomija)

**Luxembourg/Luxemburg**

UCB Pharma SA/NV

Tél/Tel: + 32 / (0)2 559 92 00

**Magyarország**

UCB Magyarország Kft.

Tel.: + 36-(1) 391 0060

**Malta**

Pharmasud Ltd.

Tel: + 356 / 21 37 64 36

**Nederland**

UCB Pharma B.V.

Tel.: + 31 / (0)76-573 11 40

**Norge**

UCB Nordic A/S

Tlf: + 45 / 32 46 24 00

**Österreich**

UCB Pharma GmbH

Tel: + 43 (0)1 291 80 00

**Polska**

UCB Pharma Sp. z o.o.

Tel: + 48 22 696 99 20

**Portugal**

UCB Pharma (Produtos Farmacêuticos), Lda

Tel: + 351 / 21 302 5300

**România**

UCB Pharma Romania S.R.L.

Tel: + 40 21 300 29 04

**Slovenija**

Medis, d.o.o.

Tel: + 386 1 589 69 00

**Slovenská republika**

UCB s.r.o., organizačná zložka

Tel: + 421 (0) 2 5920 2020

**Suomi/Finland**

UCB Pharma Oy Finland

Puh/Tel: +358 9 2514 4221

**Sverige**

UCB Nordic A/S

Tel: + 46 / (0) 40 29 49 00

**Latvija**

UCB Pharma Oy Finland  
Tel: +358 9 2514 4221 (Somija)

**United Kingdom**

UCB Pharma Ltd.  
Tel : + 44 / (0)1753 534 655

**This leaflet was last revised in {month/YYYY}**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>



## Package Leaflet: Information for the patient

### Keppra 100 mg/ml concentrate for solution for infusion

Levetiracetam

**Read all of this leaflet carefully before you or your child start using this medicine because it contains important information for you.**

- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

#### What is in this leaflet

1. What Keppra is and what it is used for
2. What you need to know before you are given Keppra
3. How Keppra is given
4. Possible side effects
5. How to store Keppra
6. Contents of the pack and other information

#### 1. What Keppra is and what it is used for

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

Keppra is used:

- on its own in adults and adolescents from 16 years of age with newly diagnosed epilepsy, to treat a certain form of epilepsy. Epilepsy is a condition where the patients have repeated fits (seizures). Levetiracetam is used for the epilepsy form in which the fits initially affect only one side of the brain, but could thereafter extend to larger areas on both sides of the brain (partial onset seizure with or without secondary generalisation). Levetiracetam has been given to you by your doctor to reduce the number of fits.
- as an add-on to other antiepileptic medicines to treat:
  - partial onset seizures with or without generalisation in adults, adolescents and children from 4 years of age
  - myoclonic seizures (short, shock-like jerks of a muscle or group of muscles) in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy.
  - primary generalised tonic-clonic seizures (major fits, including loss of consciousness) in adults and adolescents from 12 years of age with idiopathic generalised epilepsy (the type of epilepsy that is thought to have a genetic cause).

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

#### 2. What you need to know before you are given Keppra

##### Do not use Keppra

- If you are allergic to levetiracetam, pyrrolidone derivatives or any of the other ingredients of this medicine (listed in Section 6).

##### Warnings and precautions

Talk to your doctor before you are given Keppra

- If you suffer from kidney problems, follow your doctor's instructions. He/she may decide if your dose should be adjusted.
- If you notice any slow down in the growth or unexpected puberty development of your child, please contact your doctor.
- A small number of people being treated with anti-epileptics such as Keppra have had thoughts of harming or killing themselves. If you have any symptoms of depression and/or suicidal ideation, please contact your doctor.

### **Children and adolescents**

- Keppra is not indicated in children and adolescents below 16 years on its own (monotherapy)

### **Other medicines and Keppra**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Do not take macrogol (a drug used as laxative) for one hour before and one hour after taking levetiracetam as this may result in a reduction of its effect.

### **Pregnancy and breast-feeding**

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Keppra should not be used during pregnancy unless clearly necessary. A risk of birth defects for your unborn child cannot be completely excluded. 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 it 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.

### **Keppra contains sodium**

One maximum single dose of Keppra concentrate contains 2.5 mmol (or 57 mg) of sodium (0.8 mmol (or 19 mg) of sodium per vial). This should be taken into consideration if you are on a controlled sodium diet.

## **3. How Keppra is given**

A doctor or a nurse will administer you Keppra as an intravenous infusion.

Keppra must be administered twice a day, once in the morning and once in the evening, at about the same time each day.

The intravenous formulation is an alternative to your oral administration. You can switch from the film-coated tablets or from the oral solution to the intravenous formulation or reverse directly without dose adaptation. Your total daily dose and frequency of administration remain identical.

### ***Monotherapy***

#### **Dose in adults and adolescents (from 16 years of age):**

General dose: between 1000 mg and 3,000 mg each day.

When you will first start taking Keppra, your doctor will prescribe you a **lower dose** during 2 weeks before giving you the lowest general dose.

### ***Add-on therapy***

#### **Dose 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.

#### **Dose in children (4 to 11 years) and adolescents (12 to 17 years) weighing less than 50 kg:**

General dose: between 20 mg per kg bodyweight and 60 mg per kg bodyweight each day.

#### **Method and route of administration:**

Keppra is for intravenous use.

The recommended dose must be diluted in at least 100 ml of a compatible diluent and infused over 15-minutes.

For doctors and nurses, more detailed direction for the proper use of Keppra is provided in section 6.

#### **Duration of treatment:**

- 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. Should your doctor decide to stop your Keppra treatment, he/she will instruct you about the gradual withdrawal of Keppra.

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

## **4. Possible side effects**

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

#### **Tell your doctor immediately, or go to your nearest emergency department, if you experience:**

- weakness, feel light-headed or dizzy or have difficulty breathing, as these may be signs of a serious allergic (anaphylactic) reaction
- swelling of the face, lips, tongue and throat (Quincke's oedema)
- flu-like symptoms and a rash on the face followed by an extended rash with a high temperature, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia) and enlarged lymph nodes (Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS]),.
- symptoms such as low urine volume, tiredness, nausea, vomiting, confusion and swelling in the legs, ankles or feet, as this may be a sign of sudden decrease of kidney function
- a skin rash which may form blisters and look like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) (*erythema multiforme*)
- a widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (*Stevens-Johnson syndrome*)
- a more severe form of rash causing skin peeling in more than 30% of the body surface (*toxic epidermal necrolysis*)
- signs of serious mental changes or if someone around you notices signs of confusion, somnolence (sleepiness), amnesia (loss of memory), memory impairment (forgetfulness), abnormal behaviour or other neurological signs including involuntary or uncontrolled movements. These could be symptoms of an encephalopathy.

The most frequently reported adverse reactions were nasopharyngitis, somnolence (sleepiness), headache, fatigue and dizziness. At the beginning of the treatment or at dose increase side effects like

sleepiness, tiredness and dizziness may be more common. These effects should however decrease over time.

**Very common:** may affect more than 1 user in 10 people

- nasopharyngitis;
- somnolence (sleepiness), headache.

**Common:** may affect 1 to 10 users in 100 people

- anorexia (loss of appetite);
- depression, hostility or aggression, anxiety, insomnia, nervousness or irritability;
- convulsion, balance disorder (equilibrium disorder), dizziness (sensation of unsteadiness), lethargy (lack of energy and enthusiasm), tremor (involuntary trembling);
- vertigo (sensation of rotation);
- cough;
- abdominal pain, diarrhoea, dyspepsia (indigestion), vomiting, nausea;
- rash;
- asthenia/fatigue (tiredness).

**Uncommon:** may affect 1 to 10 users in 1000 people

- decreased number of blood platelets, decreased number of white blood cells;
- weight decrease, weight increase;
- suicide attempt and suicidal ideation, mental disorder, abnormal behaviour, hallucination, anger, confusion, panic attack, emotional instability/mood swings, agitation;
- amnesia (loss of memory), memory impairment (forgetfulness), abnormal coordination/ataxia (impaired coordinated movements), paraesthesia (tingling), disturbance in attention (loss of concentration);
- diplopia (double vision), vision blurred;
- elevated/abnormal values in a liver function test;
- hair loss, eczema, pruritus;
- muscle weakness, myalgia (muscle pain);
- injury.

**Rare:** may affect 1 to 10 users in 10,000 people

- infection;
- decreased number of all blood cell types;
- severe allergic reactions (DRESS, anaphylactic reaction [severe and important allergic reaction], Quincke's oedema [swelling of the face, lips, tongue and throat]);
- decreased blood sodium concentration;
- suicide, personality disorders (behavioural problems), thinking abnormal (slow thinking, unable to concentrate);
- uncontrollable muscle spasms affecting the head, torso and limbs, difficulty in controlling movements, hyperkinesia (hyperactivity);
- pancreatitis;
- liver failure, hepatitis;
- sudden decrease in kidney function
- skin rash, which may form blisters and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) (*erythema multiforme*), a widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (*Stevens-Johnson syndrome*), and a more severe form causing skin peeling in more than 30% of the body surface (*toxic epidermal necrolysis*).
- rhabdomyolysis (breakdown of muscle tissue) and associated blood creatine phosphokinase increase. Prevalence is significantly higher in Japanese patients when compared to non-Japanese patients.

## Reporting of side effects

If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Keppra

Keep this medicine out of the sight and reach of children.

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

This medicine does not require any special storage conditions.

## 6. Contents of the pack and other information

### What Keppra contains

The active substance is called levetiracetam. Each ml contains 100 mg of levetiracetam.  
The other ingredients are: sodium acetate, glacial acetic acid, sodium chloride, water for injections.

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

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

### Marketing Authorisation Holder

UCB Pharma SA, Allée de la Recherche 60, B-1070 Brussels, Belgium.

### Manufacturer

UCB Pharma SA, Chemin du Foriest, B-1420 Braine-l'Alleud, Belgium

or Aesica Pharmaceuticals S.r.l., Via Praglia, 15, I-10044 Pianezza, Italy.

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

### België/Belgique/Belgien

UCB Pharma SA/NV  
Tel/Tél: + 32 / (0)2 559 92 00

### България

Ю СИ БИ България ЕООД  
Тел.: + 359 (0) 2 962 30 49

### Česká republika

UCB s.r.o.  
Tel: + 420 221 773 411

### Danmark

UCB Nordic A/S  
Tlf: + 45 / 32 46 24 00

### Deutschland

UCB Pharma GmbH  
Tel: + 49 / (0) 2173 48 4848

### Lietuva

UCB Pharma Oy Finland  
Tel: +358 9 2514 4221 (Suomija)

### Luxembourg/Luxemburg

UCB Pharma SA/NV  
Tél/Tel: + 32 / (0)2 559 92 00

### Magyarország

UCB Magyarország Kft.  
Tel.: + 36-(1) 391 0060

### Malta

Pharmasud Ltd.  
Tel: + 356 / 21 37 64 36

### Nederland

UCB Pharma B.V.  
Tel.: + 31 / (0)76-573 11 40

**Eesti**

UCB Pharma Oy Finland  
Tel: +358 9 2514 4221 (Soome)

**Ελλάδα**

UCB A.E.  
Τηλ: + 30 / 2109974000

**España**

UCB Pharma, S.A.  
Tel: + 34 / 91 570 34 44

**France**

UCB Pharma S.A.  
Tél: + 33 / (0)1 47 29 44 35

**Hrvatska**

Medis Adria d.o.o.  
Tel: +385 (0) 1 230 34 46

**Ireland**

UCB (Pharma) Ireland Ltd.  
Tel: + 353 / (0)1-46 37 395

**Ísland**

Vistor hf.  
Tel: + 354 535 7000

**Italia**

UCB Pharma S.p.A.  
Tel: + 39 / 02 300 791

**Κύπρος**

Lifepharm (Z.A.M.) Ltd  
Τηλ: + 357 22 34 74 40

**Latvija**

UCB Pharma Oy Finland  
Tel: +358 9 2514 4221 (Somija)

**Norge**

UCB Nordic A/S  
Tlf: + 45 / 32 46 24 00

**Österreich**

UCB Pharma GmbH  
Tel: + 43 (0)1 291 80 00

**Polska**

UCB Pharma Sp. z o.o.  
Tel: + 48 22 696 99 20

**Portugal**

UCB Pharma (Produtos Farmacêuticos), Lda  
Tel: + 351 / 21 302 5300

**România**

UCB Pharma Romania S.R.L.  
Tel: + 40 21 300 29 04

**Slovenija**

Medis, d.o.o.  
Tel: + 386 1 589 69 00

**Slovenská republika**

UCB s.r.o., organizačná zložka  
Tel: + 421 (0) 2 5920 2020

**Suomi/Finland**

UCB Pharma Oy Finland  
Puh/Tel: +358 9 2514 4221

**Sverige**

UCB Nordic A/S  
Tel: + 46 / (0) 40 29 49 00

**United Kingdom**

UCB Pharma Ltd.  
Tel : + 44 / (0)1753 534 655

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**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>

**The following information is intended for healthcare professionals only:**

Directions 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

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

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 9 mg/ml (0.9%) solution for injection
- Lactated Ringer's solution for injection
- Dextrose 50 mg/ml (5%) solution for injection