

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Keppra 250 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 250 mg levetiracetam.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Keppra is indicated as adjunctive therapy

- in the treatment of partial onset seizures with or without secondary generalisation in adults, 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 (≥ 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.

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 ²)	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 (1)	-	500 to 1,000 mg once daily (2)

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

(2) Following dialysis, a 250 to 500 mg supplemental dose is recommended.

For children with renal impairment, levetiracetam dose needs to be adjusted based on the renal function as levetiracetam clearance is related to renal function. This recommendation is based on a study in adult renally impaired patients.

The CLcr in ml/min/1.73 m² 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 ²)	Dose and frequency (1)	
		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 (2) (4)	10 to 20 mg/kg (0.10 to 0.20 ml/kg) once daily (3) (5)

(1) Keppra oral solution should be used for doses under 250 mg and for patients unable to swallow tablets.

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

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

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

(5) 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 m².

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.

There are no data 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.

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 ⁽¹⁾	60 mg (0.6 ml) twice daily	180 mg (1.8 ml) twice daily
10 kg ⁽¹⁾	100 mg (1 ml) twice daily	300 mg (3 ml) twice daily
15 kg ⁽¹⁾	150 mg (1.5 ml) twice daily	450 mg (4.5 ml) twice daily
20 kg ⁽¹⁾	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 ⁽²⁾	500 mg twice daily	1,500 mg twice daily

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

⁽²⁾ 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 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.

4.4 Special warnings and precautions for use

Discontinuation

In accordance with current clinical practice, if Keppra 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).

Renal insufficiency

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

Suicide

Suicide, 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.

The safety and efficacy of levetiracetam has not been thoroughly assessed in infants with epilepsy aged less than 1 year. Only 35 infants aged less than 1 year with partial onset seizures have been exposed in clinical studies of which only 13 were aged < 6 months.

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 Keppra did not influence the serum concentrations of existing antiepileptic medicinal products (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these antiepileptic medicinal products did not influence the pharmacokinetics of Keppra.

As in adults, there is no evidence of clinically significant medicinal product interactions in paediatric patients receiving up to 60 mg/kg/day levetiracetam.

A retrospective assessment of pharmacokinetic interactions in children and adolescents with epilepsy (4 to 17 years) confirmed that adjunctive therapy with orally administered levetiracetam did not influence the steady-state serum concentrations of concomitantly administered carbamazepine and valproate. However, data suggested a 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. It is expected that other medicinal products excreted by active tubular secretion could also reduce the renal clearance of the metabolite. The effect of levetiracetam on probenecid was not studied and the effect of levetiracetam on other actively secreted medicinal products, *e.g.* NSAIDs, sulfonamides and methotrexate, is unknown.

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.

Antacids

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

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

There are no adequate data available from the use of levetiracetam in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for human is unknown. Keppra is not recommended during pregnancy and in women of childbearing potential not using contraception unless clearly necessary.

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

No studies on the effects on the ability to drive and use machines have been performed.

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

4.8 Undesirable effects

Summary of the safety profile

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

In monotherapy 49.8 % of the subjects experienced at least one drug related adverse reaction. The most frequently reported adverse reactions were fatigue and somnolence.

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

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

An increase in seizure frequency of more than 25 % was reported in 14 % of levetiracetam treated adult and paediatric patients (4 to 16 years of age) with partial onset seizures, whereas it was reported in 26 % and 21 % of placebo treated adult and paediatric patients, respectively.

When Keppra was used to treat primary generalised tonic-clonic seizures in adults and adolescents with idiopathic generalised epilepsy, there was no effect on the frequency of absences.

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. For clinical trials, the 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 $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Data from post-marketing experience are insufficient to support an estimate of their incidence in the population to be treated.

- Infections and infestations

Common: infection, nasopharyngitis

- Blood and lymphatic system disorders

Common: thrombocytopenia

Not known: leukopenia, neutropenia, pancytopenia (with bone marrow suppression identified in some of the cases)

- Metabolism and nutrition disorders

Common: anorexia, weight increase.

Not known: weight loss

- Psychiatric disorders

Common: agitation, depression, emotional lability/mood swings, hostility/aggression, insomnia, nervousness/irritability, personality disorders, thinking abnormal

Not known: abnormal behaviour, anger, anxiety, confusion, hallucination, psychotic disorder, suicide, suicide attempt and suicidal ideation

- Nervous system disorders

Very common: somnolence

Common: amnesia, ataxia, convulsion, dizziness, headache, hyperkinesia, tremor, balance disorder, disturbance in attention, memory impairment.

Not known: paraesthesia, choreoathetosis, dyskinesia

- Eye disorders

Common: diplopia, vision blurred

- Ear and labyrinth disorders

Common: vertigo

- Respiratory, thoracic and mediastinal disorders

Common: cough increased

- Gastrointestinal disorders

Common: abdominal pain, diarrhoea, dyspepsia, nausea, vomiting

Not known: pancreatitis

- Hepatobiliary disorders

Not known: hepatic failure, hepatitis, liver function test abnormal

- Skin and subcutaneous tissue disorders

Common: rash, eczema, pruritus

Not known: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme and alopecia

- Musculoskeletal and connective tissue disorders

Common: myalgia

- General disorders and administration site conditions

Very common: asthenia/fatigue

- Injury, poisoning and procedural complications

Common: accidental injury

Description of selected adverse reactions

The risk of anorexia is higher when topiramate is coadministered with levetiracetam.

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

Paediatric population

A study conducted in paediatric patients (4 to 16 years) with partial onset seizures showed that 55.4 % of the patients in the Keppra group and 40.2 % of the patients in the placebo group experienced adverse reactions. Serious adverse reactions were experienced in none of the patients in the Keppra group and 1.0 % of the patients in the placebo group. The most commonly reported adverse reactions were somnolence, hostility, nervousness, emotional lability, agitation, anorexia, asthenia and headache in the paediatric population. Safety results in paediatric patients were consistent with the safety profile of levetiracetam in adults except for behavioural and psychiatric adverse reactions which were more common in children than in adults (38.6 % versus 18.6 %). However, the relative risk was similar in children as compared to adults.

A study conducted in paediatric patients (1 month to less than 4 years) with partial onset seizures showed that 21.7 % of the patients in the Keppra group and 7.1 % of the patients in the placebo group experienced adverse reactions. No serious adverse reactions were experienced in patients in the Keppra or placebo group. During the long-term follow-up study N01148, the most frequent drug-related treatment-emergent adverse reactions in the 1 month – <4 years group were irritability (7.9 %), convulsion (7.2 %), somnolence (6.6 %), psychomotor hyperactivity (3.3 %), sleep disorder (3.3 %), and aggression (3.3 %). Safety results in paediatric patients were consistent with the safety profile of levetiracetam in older children aged 4 to 16 years.

A double-blind, placebo-controlled paediatric safety study with a non-inferiority design has assessed the cognitive and neuropsychological effects of Keppra 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 Keppra 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 Keppra 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.

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 α -ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances.

Mechanism of action

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

In vitro studies show that levetiracetam affects intraneuronal Ca²⁺ levels by partial inhibition of N-type Ca²⁺ currents and by reducing the release of Ca²⁺ from intraneuronal stores. In addition it partially reverses the reductions in GABA- and glycine-gated currents induced by zinc and β -carbolines. Furthermore, levetiracetam has been shown in *in vitro* studies to bind to a specific site in rodent brain tissue. This binding site is the synaptic vesicle protein 2A, believed to be involved in vesicle fusion and neurotransmitter exocytosis. Levetiracetam and related analogs show a rank order of affinity for binding to the synaptic vesicle protein 2A which correlates with the potency of their anti-seizure protection in the mouse audiogenic model of epilepsy. This finding suggests that the interaction between levetiracetam and the synaptic vesicle protein 2A seems to contribute to the antiepileptic mechanism of action of the medicinal product.

Pharmacodynamic effects

Levetiracetam induces seizure protection in a broad range of animal models of partial and primary generalised seizures without having a pro-convulsant effect. The primary metabolite is inactive. In man, an activity in both partial and generalised epilepsy conditions (epileptiform discharge/photoparoxysmal response) has confirmed the broad spectrum pharmacological profile of levetiracetam.

Clinical 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 b.i.d.

The primary measure of effectiveness was the responder rate (percent of patients with ≥ 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.

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 P₄₅₀ isoforms. Hydrolysis of the acetamide group was measurable in a large number of tissues including blood cells. The metabolite ucb L057 is pharmacologically inactive.

Two minor metabolites were also identified. One was obtained by hydroxylation of the pyrrolidone ring (1.6 % of the dose) and the other one by opening of the pyrrolidone ring (0.9 % of the dose). Other unidentified components accounted only for 0.6 % of the dose.

No enantiomeric interconversion was evidenced *in vivo* for either levetiracetam or its primary metabolite.

In vitro, levetiracetam and its primary metabolite have been shown not to inhibit the major human liver cytochrome P₄₅₀ isoforms (CYP3A4, 2A6, 2C9, 2C19, 2D6, 2E1 and 1A2), glucuronyl transferase (UGT1A1 AND UGT1A6) and epoxide hydroxylase activities. In addition, levetiracetam does not affect the *in vitro* glucuronidation of valproic acid.

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

Elimination

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

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

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

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

Elderly

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

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 AED.

5.3 Preclinical safety data

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

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

No adverse effects 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/m² or exposure basis) in parents and F1 generation.

Two embryo-fetal 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 fetal 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/m² basis) and 1200 mg/kg/day for fetuses.

Four embryo-fetal 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 fetal 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/m² 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/m² 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/m² basis).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Croscarmellose sodium
Macrogol 6000
Silica colloidal anhydrous
Magnesium stearate

Film-coating Opadry 85F20694:

Polyvinyl alcohol-part.hydrolyzed
Titanium dioxide (E171)
Macrogol 3350
Talc
Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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 and 200 (2 x 100) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special 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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 September 2000
Date of last renewal: 01 September 2010

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 a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Keppra is indicated as adjunctive therapy

- in the treatment of partial onset seizures with or without secondary generalisation in adults, 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 (≥ 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.

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 ²)	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 (1)	-	500 to 1,000 mg once daily (2)

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

(2) Following dialysis, a 250 to 500 mg supplemental dose is recommended.

For children with renal impairment, levetiracetam dose needs to be adjusted based on the renal function as levetiracetam clearance is related to renal function. This recommendation is based on a study in adult renally impaired patients.

The CLcr in ml/min/1.73 m² may be estimated from serum creatinine (mg/dl) determination using, 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 ²)	Dose and frequency (1)	
		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 (2) (4)	10 to 20 mg/kg (0.10 to 0.20 ml/kg) once daily (3) (5)

(1) Keppra oral solution should be used for doses under 250 mg and for patients unable to swallow tablets.

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

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

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

(5) 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 m².

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.

There are no data 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.

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 ⁽¹⁾	60 mg (0.6 ml) twice daily	180 mg (1.8 ml) twice daily
10 kg ⁽¹⁾	100 mg (1 ml) twice daily	300 mg (3 ml) twice daily
15 kg ⁽¹⁾	150 mg (1.5 ml) twice daily	450 mg (4.5 ml) twice daily
20 kg ⁽¹⁾	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 ⁽²⁾	500 mg twice daily	1,500 mg twice daily

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

⁽²⁾ 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 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.

4.4 Special warnings and precautions for use

Discontinuation

In accordance with current clinical practice, if Keppra 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).

Renal insufficiency

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

Suicide

Suicide, 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.

The safety and efficacy of levetiracetam has not been thoroughly assessed in infants with epilepsy aged less than 1 year. Only 35 infants aged less than 1 year with partial onset seizures have been exposed in clinical studies of which only 13 were aged < 6 months.

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 Keppra did not influence the serum concentrations of existing antiepileptic medicinal products (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these antiepileptic medicinal products did not influence the pharmacokinetics of Keppra.

As in adults, there is no evidence of clinically significant medicinal product interactions in paediatric patients receiving up to 60 mg/kg/day levetiracetam.

A retrospective assessment of pharmacokinetic interactions in children and adolescents with epilepsy (4 to 17 years) confirmed that adjunctive therapy with orally administered levetiracetam did not influence the steady-state serum concentrations of concomitantly administered carbamazepine and valproate. However, data suggested a 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. It is expected that other medicinal products excreted by active tubular secretion could also reduce the renal clearance of the metabolite. The effect of levetiracetam on probenecid was not studied and the effect of levetiracetam on other actively secreted medicinal products, *e.g.* NSAIDs, sulfonamides and methotrexate, is unknown.

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.

Antacids

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

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

There are no adequate data available from the use of levetiracetam in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for human is unknown. Keppra is not recommended during pregnancy and in women of childbearing potential not using contraception unless clearly necessary.

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

No studies on the effects on the ability to drive and use machines have been performed.

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

4.8 Undesirable effects

Summary of the safety profile

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

In monotherapy 49.8 % of the subjects experienced at least one drug related adverse reaction. The most frequently reported adverse reactions were fatigue and somnolence.

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

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

An increase in seizure frequency of more than 25 % was reported in 14 % of levetiracetam treated adult and paediatric patients (4 to 16 years of age) with partial onset seizures, whereas it was reported in 26 % and 21 % of placebo treated adult and paediatric patients, respectively.

When Keppra was used to treat primary generalised tonic-clonic seizures in adults and adolescents with idiopathic generalised epilepsy, there was no effect on the frequency of absences.

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. For clinical trials, the 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 $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Data from post-marketing experience are insufficient to support an estimate of their incidence in the population to be treated.

- Infections and infestations

Common: infection, nasopharyngitis

- Blood and lymphatic system disorders

Common: thrombocytopenia

Not known: leukopenia, neutropenia, pancytopenia (with bone marrow suppression identified in some of the cases)

- Metabolism and nutrition disorders

Common: anorexia, weight increase.

Not known: weight loss

- Psychiatric disorders

Common: agitation, depression, emotional lability /mood swings, hostility/aggression, insomnia, nervousness/irritability, personality disorders, thinking abnormal

Not known: abnormal behaviour, anger, anxiety, confusion, hallucination, psychotic disorder, suicide, suicide attempt and suicidal ideation

- Nervous system disorders

Very common: somnolence

Common: amnesia, ataxia, convulsion, dizziness, headache, hyperkinesia, tremor, balance disorder, disturbance in attention, memory impairment.

Not known: paraesthesia, choreoathetosis, dyskinesia

- Eye disorders

Common: diplopia, vision blurred

- Ear and labyrinth disorders

Common: vertigo

- Respiratory, thoracic and mediastinal disorders

Common: cough increased

- Gastrointestinal disorders

Common: abdominal pain, diarrhoea, dyspepsia, nausea, vomiting

Not known: pancreatitis

- Hepatobiliary disorders
Not known: hepatic failure, hepatitis, liver function test abnormal
- Skin and subcutaneous tissue disorders
Common: rash, eczema, pruritus
Not known: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme and alopecia
- Musculoskeletal and connective tissue disorders
Common: myalgia
- General disorders and administration site conditions
Very common: asthenia/fatigue.
- Injury, poisoning and procedural complications
Common: accidental injury

Description of selected adverse reactions

The risk of anorexia is higher when topiramate is coadministered with levetiracetam.
In several cases of alopecia, recovery was observed when levetiracetam was discontinued.

Paediatric population

A study conducted in paediatric patients (4 to 16 years) with partial onset seizures showed that 55.4 % of the patients in the Keppra group and 40.2 % of the patients in the placebo group experienced adverse reactions. Serious adverse reactions were experienced in none of the patients in the Keppra group and 1.0 % of the patients in the placebo group. The most commonly reported adverse reactions were somnolence, hostility, nervousness, emotional lability, agitation, anorexia, asthenia and headache in the paediatric population. Safety results in paediatric patients were consistent with the safety profile of levetiracetam in adults except for behavioural and psychiatric adverse reactions which were more common in children than in adults (38.6 % versus 18.6 %). However, the relative risk was similar in children as compared to adults.

A study conducted in paediatric patients (1 month to less than 4 years) with partial onset seizures showed that 21.7 % of the patients in the Keppra group and 7.1 % of the patients in the placebo group experienced adverse reactions. No serious adverse reactions were experienced in patients in the Keppra or placebo group. During the long-term follow-up study N01148, the most frequent drug-related treatment-emergent adverse reactions in the 1 month – <4 years group were irritability (7.9 %), convulsion (7.2 %), somnolence (6.6 %), psychomotor hyperactivity (3.3 %), sleep disorder (3.3 %), and aggression (3.3 %). Safety results in paediatric patients were consistent with the safety profile of levetiracetam in older children aged 4 to 16 years.

A double-blind, placebo-controlled paediatric safety study with a non-inferiority design has assessed the cognitive and neuropsychological effects of Keppra 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 Keppra 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 Keppra 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.

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 α -ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances.

Mechanism of action

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

In vitro studies show that levetiracetam affects intraneuronal Ca²⁺ levels by partial inhibition of N-type Ca²⁺ currents and by reducing the release of Ca²⁺ from intraneuronal stores. In addition it partially reverses the reductions in GABA- and glycine-gated currents induced by zinc and β -carbolines. Furthermore, levetiracetam has been shown in *in vitro* studies to bind to a specific site in rodent brain tissue. This binding site is the synaptic vesicle protein 2A, believed to be involved in vesicle fusion and neurotransmitter exocytosis. Levetiracetam and related analogs show a rank order of affinity for binding to the synaptic vesicle protein 2A which correlates with the potency of their anti-seizure protection in the mouse audiogenic model of epilepsy. This finding suggests that the interaction between levetiracetam and the synaptic vesicle protein 2A seems to contribute to the antiepileptic mechanism of action of the medicinal product.

Pharmacodynamic effects

Levetiracetam induces seizure protection in a broad range of animal models of partial and primary generalised seizures without having a pro-convulsant effect. The primary metabolite is inactive. In man, an activity in both partial and generalised epilepsy conditions (epileptiform discharge/photoparoxysmal response) has confirmed the broad spectrum pharmacological profile of levetiracetam.

Clinical 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 b.i.d.

The primary measure of effectiveness was the responder rate (percent of patients with ≥ 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.

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 P₄₅₀ isoforms. Hydrolysis of the acetamide group was measurable in a large number of tissues including blood cells. The metabolite ucb L057 is pharmacologically inactive.

Two minor metabolites were also identified. One was obtained by hydroxylation of the pyrrolidone ring (1.6 % of the dose) and the other one by opening of the pyrrolidone ring (0.9 % of the dose). Other unidentified components accounted only for 0.6 % of the dose.

No enantiomeric interconversion was evidenced *in vivo* for either levetiracetam or its primary metabolite.

In vitro, levetiracetam and its primary metabolite have been shown not to inhibit the major human liver cytochrome P₄₅₀ isoforms (CYP3A4, 2A6, 2C9, 2C19, 2D6, 2E1 and 1A2), glucuronyl transferase (UGT1A1 and UGT1A6) and epoxide hydroxylase activities. In addition, levetiracetam does not affect the *in vitro* glucuronidation of valproic acid.

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

Elimination

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

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

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

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

Elderly

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

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 AED.

5.3 Preclinical safety data

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

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

No adverse effects 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/m² or exposure basis) in parents and F1 generation.

Two embryo-fetal 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 fetal 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/m² basis) and 1200 mg/kg/day for fetuses.

Four embryo-fetal 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 fetal 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/m² 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/m² 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/m² basis)

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Croscarmellose sodium
Macrogol 6000
Silica colloidal anhydrous
Magnesium stearate

Film-coating Opadry 85F32004:

Polyvinyl alcohol-part. hydrolyzed
Titanium dioxide (E171)
Macrogol 3350
Talc
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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 and 200 (2 x 100) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special 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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 September 2000
Date of last renewal: 01 September 2010

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:

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

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Kepra is indicated as adjunctive therapy

- in the treatment of partial onset seizures with or without secondary generalisation in adults, 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 (≥ 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.

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 ²)	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 (1)	-	500 to 1,000 mg once daily (2)

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

(2) Following dialysis, a 250 to 500 mg supplemental dose is recommended.

For children with renal impairment, levetiracetam dose needs to be adjusted based on the renal function as levetiracetam clearance is related to renal function. This recommendation is based on a study in adult renally impaired patients.

The CLcr in ml/min/1.73 m² may be estimated from serum creatinine (mg/dl) determination using, 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 ²)	Dose and frequency (1)	
		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 (2) (4)	10 to 20 mg/kg (0.10 to 0.20 ml/kg) once daily (3) (5)

(1) Keppra oral solution should be used for doses under 250 mg and for patients unable to swallow tablets.

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

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

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

(5) 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 m².

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.

There are no data 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.

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 ⁽¹⁾	60 mg (0.6 ml) twice daily	180 mg (1.8 ml) twice daily
10 kg ⁽¹⁾	100 mg (1 ml) twice daily	300 mg (3 ml) twice daily
15 kg ⁽¹⁾	150 mg (1.5 ml) twice daily	450 mg (4.5 ml) twice daily
20 kg ⁽¹⁾	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 ⁽²⁾	500 mg twice daily	1,500 mg twice daily

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

⁽²⁾ 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 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.

4.4 Special warnings and precautions for use

Discontinuation

In accordance with current clinical practice, if Keppra 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).

Renal insufficiency

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

Suicide

Suicide, 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.

The safety and efficacy of levetiracetam has not been thoroughly assessed in infants with epilepsy aged less than 1 year. Only 35 infants aged less than 1 year with partial onset seizures have been exposed in clinical studies of which only 13 were aged < 6 months.

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 Keppra did not influence the serum concentrations of existing antiepileptic medicinal products (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these antiepileptic medicinal products did not influence the pharmacokinetics of Keppra.

As in adults, there is no evidence of clinically significant medicinal product interactions in paediatric patients receiving up to 60 mg/kg/day levetiracetam.

A retrospective assessment of pharmacokinetic interactions in children and adolescents with epilepsy (4 to 17 years) confirmed that adjunctive therapy with orally administered levetiracetam did not influence the steady-state serum concentrations of concomitantly administered carbamazepine and valproate. However, data suggested a 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. It is expected that other medicinal products excreted by active tubular secretion could also reduce the renal clearance of the metabolite. The effect of levetiracetam on probenecid was not studied and the effect of levetiracetam on other actively secreted medicinal products, *e.g.* NSAIDs, sulfonamides and methotrexate, is unknown.

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.

Antacids

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

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

There are no adequate data available from the use of levetiracetam in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for human is unknown. Keppra is not recommended during pregnancy and in women of childbearing potential not using contraception unless clearly necessary.

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

No studies on the effects on the ability to drive and use machines have been performed.

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

4.8 Undesirable effects

Summary of the safety profile

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

In monotherapy 49.8 % of the subjects experienced at least one drug related adverse reaction. The most frequently reported adverse reactions were fatigue and somnolence.

A study conducted in adults and adolescents with myoclonic seizures (12 to 65 years) showed that 33.3 % of the patients in the Keppra group and 30.0 % of the patients in the placebo group experienced adverse reactions that were judged to be related to treatment. The most commonly reported adverse reactions were headache and somnolence. The incidence of adverse reactions in

patients with myoclonic seizures was lower than that in adult patients with partial onset seizures (33.3 % versus 46.4 %).

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

An increase in seizure frequency of more than 25 % was reported in 14 % of levetiracetam treated adult and paediatric patients (4 to 16 years of age) with partial onset seizures, whereas it was reported in 26 % and 21 % of placebo treated adult and paediatric patients, respectively.

When Keppra was used to treat primary generalised tonic-clonic seizures in adults and adolescents with idiopathic generalised epilepsy, there was no effect on the frequency of absences.

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. For clinical trials, the 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 $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Data from post-marketing experience are insufficient to support an estimate of their incidence in the population to be treated.

- Infections and infestations

Common: infection, nasopharyngitis

- Blood and lymphatic system disorders

Common: thrombocytopenia

Not known: leukopenia, neutropenia, pancytopenia (with bone marrow suppression identified in some of the cases)

- Metabolism and nutrition disorders

Common: anorexia, weight increase.

Not known: weight loss

- Psychiatric disorders

Common: agitation, depression, emotional lability/mood swings, hostility/aggression, insomnia, nervousness/irritability, personality disorders, thinking abnormal

Not known: abnormal behaviour, anger, anxiety, confusion, hallucination, psychotic disorder, suicide, suicide attempt and suicidal ideation

- Nervous system disorders

Very common: somnolence

Common: amnesia, ataxia, convulsion, dizziness, headache, hyperkinesia, tremor, balance disorder, disturbance in attention, memory impairment.

Not known: paraesthesia, choreoathetosis, dyskinesia

- Eye disorders

Common: diplopia, vision blurred

- Ear and labyrinth disorders

Common: vertigo

- Respiratory, thoracic and mediastinal disorders

Common: cough increased

- Gastrointestinal disorders
Common: abdominal pain, diarrhoea, dyspepsia, nausea, vomiting
Not known: pancreatitis
- Hepatobiliary disorders
Not known: hepatic failure, hepatitis, liver function test abnormal
- Skin and subcutaneous tissue disorders
Common: rash, eczema, pruritus
Not known: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme and alopecia
- Musculoskeletal and connective tissue disorders
Common: myalgia
- General disorders and administration site conditions
Very common: asthenia/fatigue.
- Injury, poisoning and procedural complications
Common: accidental injury

Description of selected adverse reactions

The risk of anorexia is higher when topiramate is coadministered with levetiracetam.
In several cases of alopecia, recovery was observed when levetiracetam was discontinued.

Paediatric population

A study conducted in paediatric patients (4 to 16 years) with partial onset seizures showed that 55.4 % of the patients in the Keppra group and 40.2 % of the patients in the placebo group experienced adverse reactions. Serious adverse reactions were experienced in none of the patients in the Keppra group and 1.0 % of the patients in the placebo group. The most commonly reported adverse reactions were somnolence, hostility, nervousness, emotional lability, agitation, anorexia, asthenia and headache in the paediatric population. Safety results in paediatric patients were consistent with the safety profile of levetiracetam in adults except for behavioural and psychiatric adverse reactions which were more common in children than in adults (38.6 % versus 18.6 %). However, the relative risk was similar in children as compared to adults.

A study conducted in paediatric patients (1 month to less than 4 years) with partial onset seizures showed that 21.7 % of the patients in the Keppra group and 7.1 % of the patients in the placebo group experienced adverse reactions. No serious undesirable effects were experienced in patients in the Keppra or placebo group. During the long-term follow-up study N01148, the most frequent drug-related treatment-emergent adverse reactions in the 1 month – <4 years group were irritability (7.9 %), convulsion (7.2 %), somnolence (6.6 %), psychomotor hyperactivity (3.3 %), sleep disorder (3.3 %), and aggression (3.3 %). Safety results in paediatric patients were consistent with the safety profile of levetiracetam in older children aged 4 to 16 years.

A double-blind, placebo-controlled paediatric safety study with a non-inferiority design has assessed the cognitive and neuropsychological effects of Keppra 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 Keppra 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 Keppra 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.

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 α -ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances.

Mechanism of action

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

In vitro studies show that levetiracetam affects intraneuronal Ca^{2+} levels by partial inhibition of N-type Ca^{2+} currents and by reducing the release of Ca^{2+} from intraneuronal stores. In addition it partially reverses the reductions in GABA- and glycine-gated currents induced by zinc and β -carbolines. Furthermore, levetiracetam has been shown in *in vitro* studies to bind to a specific site in rodent brain tissue. This binding site is the synaptic vesicle protein 2A, believed to be involved in vesicle fusion and neurotransmitter exocytosis. Levetiracetam and related 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 b.i.d.

The primary measure of effectiveness was the responder rate (percent of patients with ≥ 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.

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 P₄₅₀ isoforms. Hydrolysis of the acetamide group was measurable in a large number of tissues including blood cells. The metabolite ucb L057 is pharmacologically inactive.

Two minor metabolites were also identified. One was obtained by hydroxylation of the pyrrolidone ring (1.6 % of the dose) and the other one by opening of the pyrrolidone ring (0.9 % of the dose). Other unidentified components accounted only for 0.6 % of the dose.

No enantiomeric interconversion was evidenced *in vivo* for either levetiracetam or its primary metabolite.

In vitro, levetiracetam and its primary metabolite have been shown not to inhibit the major human liver cytochrome P₄₅₀ isoforms (CYP3A4, 2A6, 2C9, 2C19, 2D6, 2E1 and 1A2), glucuronyl transferase (UGT1A1 and UGT1A6) and epoxide hydroxylase activities. In addition, levetiracetam does not affect the *in vitro* glucuronidation of valproic acid.

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

Elimination

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

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

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

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

Elderly

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

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 AED.

5.3 Preclinical safety data

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

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

No adverse effects 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/m² or exposure basis) in parents and F1 generation.

Two embryo-fetal 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

fetal 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/m² basis) and 1200 mg/kg/day for fetuses.

Four embryo-fetal 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 fetal 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/m² 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/m² 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/m² basis)

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Croscarmellose sodium

Macrogol 6000

Silica colloidal anhydrous.

Magnesium stearate

Film-coating Opadry 85F23452:

Polyvinyl alcohol-part. hydrolyzed

Titanium dioxide (E171)

Macrogol 3350

Talc

Sunset yellow FCF aluminium lake (E110)

Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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 and 200 (2 x 100) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special 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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 September 2000
Date of last renewal: 01 September 2010

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 1000 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Keppra is indicated as adjunctive therapy

- in the treatment of partial onset seizures with or without secondary generalisation in adults, 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 (≥ 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.

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 weighting more than 50 kg with impaired renal function:

Group	Creatinine clearance (ml/min/1.73m ²)	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 (1)	-	500 to 1,000 mg once daily (2)

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

(2) Following dialysis, a 250 to 500 mg supplemental dose is recommended.

For children with renal impairment, levetiracetam dose needs to be adjusted based on the renal function as levetiracetam clearance is related to renal function. This recommendation is based on a study in adult renally impaired patients.

The CLcr in ml/min/1.73 m² may be estimated from serum creatinine (mg/dl) determination using, 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 ²)	Dose and frequency (1)	
		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 (2) (4)	10 to 20 mg/kg (0.10 to 0.20 ml/kg) once daily (3) (5)

(1) Keppra oral solution should be used for doses under 250 mg and for patients unable to swallow tablets.

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

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

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

(5) 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 m².

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.

There are no data 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.

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 ⁽¹⁾	60 mg (0.6 ml) twice daily	180 mg (1.8 ml) twice daily
10 kg ⁽¹⁾	100 mg (1 ml) twice daily	300 mg (3 ml) twice daily
15 kg ⁽¹⁾	150 mg (1.5 ml) twice daily	450 mg (4.5 ml) twice daily
20 kg ⁽¹⁾	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 ⁽²⁾	500 mg twice daily	1,500 mg twice daily

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

⁽²⁾ 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 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.

4.4 Special warnings and precautions for use

Discontinuation

In accordance with current clinical practice, if Keppra 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).

Renal insufficiency

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

Suicide

Suicide, 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.

The safety and efficacy of levetiracetam has not been thoroughly assessed in infants with epilepsy aged less than 1 year. Only 35 infants aged less than 1 year with partial onset seizures have been exposed in clinical studies of which only 13 were aged < 6 months.

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 Keppra did not influence the serum concentrations of existing antiepileptic medicinal products (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these antiepileptic medicinal products did not influence the pharmacokinetics of Keppra.

As in adults, there is no evidence of clinically significant medicinal product interactions in paediatric patients receiving up to 60 mg/kg/day levetiracetam.

A retrospective assessment of pharmacokinetic interactions in children and adolescents with epilepsy (4 to 17 years) confirmed that adjunctive therapy with orally administered levetiracetam did not influence the steady-state serum concentrations of concomitantly administered carbamazepine and valproate. However, data suggested a 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. It is expected that other medicinal products excreted by active tubular secretion could also reduce the renal clearance of the metabolite. The effect of levetiracetam on probenecid was not studied and the effect of levetiracetam on other actively secreted medicinal products, *e.g.* NSAIDs, sulfonamides and methotrexate, is unknown.

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.

Antacids

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

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

There are no adequate data available from the use of levetiracetam in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for human is unknown. Keppra is not recommended during pregnancy and in women of childbearing potential not using contraception unless clearly necessary.

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

No studies on the effects on the ability to drive and use machines have been performed.

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

4.8 Undesirable effects

Summary of the safety profile

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

In monotherapy 49.8 % of the subjects experienced at least one drug related adverse reaction. The most frequently reported adverse reactions were fatigue and somnolence.

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

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

An increase in seizure frequency of more than 25 % was reported in 14 % of levetiracetam treated adult and paediatric patients (4 to 16 years of age) with partial onset seizures, whereas it was reported in 26 % and 21 % of placebo treated adult and paediatric patients, respectively.

When Keppra was used to treat primary generalised tonic-clonic seizures in adults and adolescents with idiopathic generalised epilepsy, there was no effect on the frequency of absences.

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. For clinical trials, the 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 $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Data from post-marketing experience are insufficient to support an estimate of their incidence in the population to be treated.

- Infections and infestations

Common: infection, nasopharyngitis

- Blood and lymphatic system disorders

Common: thrombocytopenia

Not known: leukopenia, neutropenia, pancytopenia (with bone marrow suppression identified in some of the cases)

- Metabolism and nutrition disorders

Common: anorexia, weight increase.

Not known: weight loss

- Psychiatric disorders

Common: agitation, depression, emotional lability/mood swings, hostility/aggression, insomnia, nervousness/irritability, personality disorders, thinking abnormal

Not known: abnormal behaviour, anger, anxiety, confusion, hallucination, psychotic disorder, suicide, suicide attempt and suicidal ideation

- Nervous system disorders

Very common: somnolence

Common: amnesia, ataxia, convulsion, dizziness, headache, hyperkinesia, tremor, balance disorder, disturbance in attention, memory impairment.

Not known: paraesthesia, choreoathetosis, dyskinesia

- Eye disorders

Common: diplopia, vision blurred

- Ear and labyrinth disorders

Common: vertigo

- Respiratory, thoracic and mediastinal disorders

Common: cough increased

- Gastrointestinal disorders

Common: abdominal pain, diarrhoea, dyspepsia, nausea, vomiting

Not known: pancreatitis

- Hepatobiliary disorders

Not known: hepatic failure, hepatitis, liver function test abnormal

- Skin and subcutaneous tissue disorders

Common: rash, eczema, pruritus

Not known: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme and alopecia

- Musculoskeletal and connective tissue disorders

Common: myalgia

- General disorders and administration site conditions

Very common: asthenia/fatigue.

- Injury, poisoning and procedural complications

Common: accidental injury

Description of selected adverse reactions

The risk of anorexia is higher when topiramate is coadministered with levetiracetam.

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

Paediatric population

A study conducted in paediatric patients (4 to 16 years) with partial onset seizures showed that 55.4 % of the patients in the Keppra group and 40.2 % of the patients in the placebo group experienced adverse reactions. Serious adverse reactions were experienced in none of the patients in the Keppra group and 1.0 % of the patients in the placebo group. The most commonly reported adverse reactions were somnolence, hostility, nervousness, emotional lability, agitation, anorexia, asthenia and headache in the paediatric population. Safety results in paediatric patients were consistent with the safety profile of levetiracetam in adults except for behavioural and psychiatric adverse reactions which were more common in children than in adults (38.6 % versus 18.6 %). However, the relative risk was similar in children as compared to adults.

A study conducted in paediatric patients (1 month to less than 4 years) with partial onset seizures showed that 21.7 % of the patients in the Keppra group and 7.1 % of the patients in the placebo group experienced adverse reactions. No serious adverse reactions were experienced in patients in the Keppra or placebo group. During the long-term follow-up study N01148, the most frequent drug-related treatment-emergent adverse reactions in the 1 month – <4 years group were irritability (7.9 %), convulsion (7.2 %), somnolence (6.6 %), psychomotor hyperactivity (3.3 %), sleep disorder (3.3 %), and aggression (3.3 %). Safety results in paediatric patients were consistent with the safety profile of levetiracetam in older children aged 4 to 16 years.

A double-blind, placebo-controlled paediatric safety study with a non-inferiority design has assessed the cognitive and neuropsychological effects of Keppra 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 Keppra 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 Keppra 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.

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 α -ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances.

Mechanism of action

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

In vitro studies show that levetiracetam affects intraneuronal Ca²⁺ levels by partial inhibition of N-type Ca²⁺ currents and by reducing the release of Ca²⁺ from intraneuronal stores. In addition it partially reverses the reductions in GABA- and glycine-gated currents induced by zinc and β -carbolines. Furthermore, levetiracetam has been shown in *in vitro* studies to bind to a specific site in rodent brain tissue. This binding site is the synaptic vesicle protein 2A, believed to be involved in vesicle fusion and neurotransmitter exocytosis. Levetiracetam and related analogs show a rank order of affinity for binding to the synaptic vesicle protein 2A which correlates with the potency of their anti-seizure protection in the mouse audiogenic model of epilepsy. This finding suggests that the interaction between levetiracetam and the synaptic vesicle protein 2A seems to contribute to the antiepileptic mechanism of action of the medicinal product.

Pharmacodynamic effects

Levetiracetam induces seizure protection in a broad range of animal models of partial and primary generalised seizures without having a pro-convulsant effect. The primary metabolite is inactive. In man, an activity in both partial and generalised epilepsy conditions (epileptiform discharge/photoparoxysmal response) has confirmed the broad spectrum pharmacological profile of levetiracetam.

Clinical 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 b.i.d.

The primary measure of effectiveness was the responder rate (percent of patients with ≥ 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.

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 P₄₅₀ isoforms. Hydrolysis of the acetamide group was measurable in a large number of tissues including blood cells. The metabolite ucb L057 is pharmacologically inactive.

Two minor metabolites were also identified. One was obtained by hydroxylation of the pyrrolidone ring (1.6 % of the dose) and the other one by opening of the pyrrolidone ring (0.9 % of the dose). Other unidentified components accounted only for 0.6 % of the dose.

No enantiomeric interconversion was evidenced *in vivo* for either levetiracetam or its primary metabolite.

In vitro, levetiracetam and its primary metabolite have been shown not to inhibit the major human liver cytochrome P₄₅₀ isoforms (CYP3A4, 2A6, 2C9, 2C19, 2D6, 2E1 and 1A2), glucuronyl transferase (UGT1A1 and UGT1A6) and epoxide hydroxylase activities. In addition, levetiracetam does not affect the *in vitro* glucuronidation of valproic acid.

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

Elimination

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

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

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

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

Elderly

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

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 AED.

5.3 Preclinical safety data

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

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

No adverse effects 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/m² or exposure basis) in parents and F1 generation.

Two embryo-fetal 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 fetal 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/m² basis) and 1200 mg/kg/day for fetuses.

Four embryo-fetal 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 fetal 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/m² 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/m² 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/m² basis)

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Croscarmellose sodium

Macrogol 6000

Silica colloidal anhydrous

Magnesium stearate

Film-coating Opadry 85F18422:

Polyvinyl alcohol-part. hydrolyzed

Titanium dioxide (E171)

Macrogol 3350

Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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 and 200 (2 x 100) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special 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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 September 2000
Date of last renewal: 01 September 2010

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:

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

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.

Clear liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Keppra is indicated as adjunctive therapy

- in the treatment of partial onset seizures with or without secondary generalisation in adults, 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 (≥ 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.

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 ²)	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 (1)	-	500 to 1,000 mg once daily (2)

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

(2) Following dialysis, a 250 to 500 mg supplemental dose is recommended.

For children with renal impairment, levetiracetam dose needs to be adjusted based on the renal function as levetiracetam clearance is related to renal function. This recommendation is based on a study in adult renally impaired patients.

The CLcr in ml/min/1.73 m² may be estimated from serum creatinine (mg/dl) determination using, 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 ²)	Dose and frequency (1)	
		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 (2) (4)	10 to 20 mg/kg (0.10 to 0.20 ml/kg) once daily (3) (5)

(1) Keppra oral solution should be used for doses under 250 mg and for patients unable to swallow tablets.

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

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

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

(5) 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 m².

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.

There are no data 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 ⁽¹⁾	60 mg (0.6 ml) twice daily	180 mg (1.8 ml) twice daily
10 kg ⁽¹⁾	100 mg (1 ml) twice daily	300 mg (3 ml) twice daily
15 kg ⁽¹⁾	150 mg (1.5 ml) twice daily	450 mg (4.5 ml) twice daily
20 kg ⁽¹⁾	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 ⁽²⁾	500 mg twice daily	1,500 mg twice daily

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

⁽²⁾ 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 (containing 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 (containing 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 (containing 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. A graduated oral syringe, an adaptor for the syringe and instructions for use in the package leaflet are provided with Keppra.

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.

4.4 Special warnings and precautions for use

Discontinuation

In accordance with current clinical practice, if Keppra 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).

Renal insufficiency

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

Suicide

Suicide, 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.

The safety and efficacy of levetiracetam has not been thoroughly assessed in infants with epilepsy aged less than 1 year. Only 35 infants aged less than 1 year with partial onset seizures have been exposed in clinical studies of which only 13 were aged < 6 months.

Excipients

Keppra 100 mg/ml oral solution includes methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) which may cause allergic reactions (possibly delayed). It also includes maltitol 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 Keppra did not influence the serum concentrations of existing antiepileptic medicinal products (phenytoin, carbamazepine, valproic

acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these antiepileptic medicinal products did not influence the pharmacokinetics of Keppra.

As in adults, there is no evidence of clinically significant medicinal product interactions in paediatric patients receiving up to 60 mg/kg/day levetiracetam.

A retrospective assessment of pharmacokinetic interactions in children and adolescents with epilepsy (4 to 17 years) confirmed that adjunctive therapy with orally administered levetiracetam did not influence the steady-state serum concentrations of concomitantly administered carbamazepine and valproate. However, data suggested a 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. It is expected that other medicinal products excreted by active tubular secretion could also reduce the renal clearance of the metabolite. The effect of levetiracetam on probenecid was not studied and the effect of levetiracetam on other actively secreted medicinal products, *e.g.* NSAIDs, sulfonamides and methotrexate, is unknown.

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.

Antacids

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

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

There are no adequate data available from the use of levetiracetam in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for human is unknown. Keppra is not recommended during pregnancy and in women of childbearing potential not using contraception unless clearly necessary.

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

No studies on the effects on the ability to drive and use machines have been performed. Due to possible different individual sensitivity, some patients might experience somnolence or other central nervous system related symptoms, especially at the beginning of treatment or following a dose increase. Therefore, caution is recommended in those patients when performing skilled tasks, e.g. driving vehicles or operating machinery. Patients are advised not to drive or use machines until it is established that their ability to perform such activities is not affected.

4.8 Undesirable effects

Summary of the safety profile

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

In monotherapy 49.8 % of the subjects experienced at least one drug related adverse reaction. The most frequently reported adverse reactions were fatigue and somnolence.

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

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

An increase in seizure frequency of more than 25 % was reported in 14 % of levetiracetam treated adult and paediatric patients (4 to 16 years of age) with partial onset seizures, whereas it was reported in 26 % and 21 % of placebo treated adult and paediatric patients, respectively.

When Keppra was used to treat primary generalised tonic-clonic seizures in adults and adolescents with idiopathic generalised epilepsy, there was no effect on the frequency of absences.

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. For clinical trials, the 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 $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Data from post-marketing experience are insufficient to support an estimate of their incidence in the population to be treated.

- Infections and infestations
Common: infection, nasopharyngitis

- Blood and lymphatic system disorders
Common: thrombocytopenia
Not known: leukopenia, neutropenia, pancytopenia (with bone marrow suppression identified in some of the cases).
- Metabolism and nutrition disorders
Common: anorexia, weight increase.
Not known: weight loss
- Psychiatric disorders
Common: agitation, depression, emotional lability/mood swings, hostility/aggression, insomnia, nervousness/irritability, personality disorders, thinking abnormal
Not known: abnormal behaviour, anger, anxiety, confusion, hallucination, psychotic disorder, suicide, suicide attempt and suicidal ideation
- Nervous system disorders
Very common: somnolence
Common: amnesia, ataxia, convulsion, dizziness, headache, hyperkinesia, tremor, balance disorder, disturbance in attention, memory impairment.
Not known: paraesthesia, choreoathetosis, dyskinesia
- Eye disorders
Common: diplopia, vision blurred
- Ear and labyrinth disorders
Common: vertigo
- Respiratory, thoracic and mediastinal disorders
Common: cough increased
- Gastrointestinal disorders
Common: abdominal pain, diarrhoea, dyspepsia, nausea, vomiting
Not known: pancreatitis
- Hepatobiliary disorders
Not known: hepatic failure, hepatitis, liver function test abnormal
- Skin and subcutaneous tissue disorders
Common: rash, eczema, pruritus
Not known: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme and alopecia
- Musculoskeletal and connective tissue disorders
Common: myalgia
- General disorders and administration site conditions
Very common: asthenia/fatigue.
- Injury, poisoning and procedural complications
Common: accidental injury

Description of selected adverse reactions

The risk of anorexia is higher when topiramate is coadministered with levetiracetam.
In several cases of alopecia, recovery was observed when levetiracetam was discontinued.

Paediatric population

A study conducted in paediatric patients (4 to 16 years) with partial onset seizures showed that 55.4 % of the patients in the Keppra group and 40.2 % of the patients in the placebo group experienced adverse reactions. Serious adverse reactions were experienced in none of the patients in the Keppra group and 1.0 % of the patients in the placebo group. The most commonly reported adverse reactions were somnolence, hostility, nervousness, emotional lability, agitation, anorexia, asthenia and headache in the paediatric population. Safety results in paediatric patients were consistent with the safety profile of levetiracetam in adults except for behavioural and psychiatric adverse reactions which were more common in children than in adults (38.6 % versus 18.6 %). However, the relative risk was similar in children as compared to adults.

A study conducted in paediatric patients (1 month to less than 4 years) with partial onset seizures showed that 21.7 % of the patients in the Keppra group and 7.1 % of the patients in the placebo group experienced adverse reactions. No serious adverse reactions were experienced in patients in the Keppra or placebo group. During the long-term follow-up study N01148, the most frequent drug-related treatment-emergent adverse reactions in the 1 month – <4 years group were irritability (7.9 %), convulsion (7.2 %), somnolence (6.6 %), psychomotor hyperactivity (3.3 %), sleep disorder (3.3 %), and aggression (3.3 %). Safety results in paediatric patients were consistent with the safety profile of levetiracetam in older children aged 4 to 16 years.

A double-blind, placebo-controlled paediatric safety study with a non-inferiority design has assessed the cognitive and neuropsychological effects of Keppra 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 Keppra 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 Keppra 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.

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 α -ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances.

Mechanism of action

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

In vitro studies show that levetiracetam affects intraneuronal Ca²⁺ levels by partial inhibition of N-type Ca²⁺ currents and by reducing the release of Ca²⁺ from intraneuronal stores. In addition it partially reverses the reductions in GABA- and glycine-gated currents induced by zinc and β -carbolines. Furthermore, levetiracetam has been shown in *in vitro* studies to bind to a specific site in rodent brain tissue. This binding site is the synaptic vesicle protein 2A, believed to be involved in vesicle fusion and neurotransmitter exocytosis. Levetiracetam and related analogs show a rank order of affinity for binding to the synaptic vesicle protein 2A which correlates with the potency of their anti-seizure protection in the mouse audiogenic model of epilepsy. This finding suggests that the interaction between levetiracetam and the synaptic vesicle protein 2A seems to contribute to the antiepileptic mechanism of action of the medicinal product.

Pharmacodynamic effects

Levetiracetam induces seizure protection in a broad range of animal models of partial and primary generalised seizures without having a pro-convulsant effect. The primary metabolite is inactive. In man, an activity in both partial and generalised epilepsy conditions (epileptiform discharge/photoparoxysmal response) has confirmed the broad spectrum pharmacological profile of levetiracetam.

Clinical 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 b.i.d.

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.

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

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

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

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

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

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

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

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

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

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

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

5.2 Pharmacokinetic properties

Levetiracetam is a highly soluble and permeable compound. The pharmacokinetic profile is linear with low intra- and inter-subject variability. There is no modification of the clearance after repeated

administration. There is no evidence for any relevant gender, race or circadian variability. The pharmacokinetic profile is comparable in healthy volunteers and in patients with epilepsy.

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

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

Adults and adolescents

Absorption

Levetiracetam is rapidly absorbed after oral administration. Oral absolute bioavailability is close to 100 %.

Peak plasma concentrations (C_{max}) are achieved at 1.3 hours after dosing. Steady-state is achieved after two days of a twice daily administration schedule.

Peak concentrations (C_{max}) are typically 31 and 43 µg/ml following a single 1,000 mg dose and repeated 1,000 mg twice daily dose, respectively.

The extent of absorption is dose-independent and is not altered by food.

Distribution

No tissue distribution data are available in humans.

Neither levetiracetam nor its primary metabolite are significantly bound to plasma proteins (< 10 %).

The volume of distribution of levetiracetam is approximately 0.5 to 0.7 l/kg, a value close to the total body water volume.

Biotransformation

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

Two minor metabolites were also identified. One was obtained by hydroxylation of the pyrrolidone ring (1.6 % of the dose) and the other one by opening of the pyrrolidone ring (0.9 % of the dose).

Other unidentified components accounted only for 0.6 % of the dose.

No enantiomeric interconversion was evidenced *in vivo* for either levetiracetam or its primary metabolite.

In vitro, levetiracetam and its primary metabolite have been shown not to inhibit the major human liver cytochrome P₄₅₀ isoforms (CYP3A4, 2A6, 2C9, 2C19, 2D6, 2E1 and 1A2), glucuronyl transferase (UGT1A1 and UGT1A6) and epoxide hydroxylase activities. In addition, levetiracetam does not affect the *in vitro* glucuronidation of valproic acid.

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

Elimination

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

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

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

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

Elderly

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

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 AED.

5.3 Preclinical safety data

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

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

No adverse effects 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/m² or exposure basis) in parents and F1 generation.

Two embryo-fetal 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 fetal 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/m² basis) and 1200 mg/kg/day for fetuses.

Four embryo-fetal 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 fetal 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/m² 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/m² 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/m² 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 container 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

No special 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 last renewal: 01 September 2010

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 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.

Excipients:

Each dose contains 57 mg of sodium.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear, colourless, concentrate.

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 patients 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 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.

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

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 (≥ 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.

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 ²)	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 (1)	-	500 to 1,000 mg once daily (2)

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

(2) Following dialysis, a 250 to 500 mg supplemental dose is recommended.

For children with renal impairment, levetiracetam dose needs to be adjusted based on the renal function as levetiracetam clearance is related to renal function. This recommendation is based on a study in adult renally impaired patients.

The CLcr in ml/min/1.73 m² may be estimated from serum creatinine (mg/dl) determination using, for young adolescents and children 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= 0.55 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 ²)	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 (1) (2)

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

(2) 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 m².

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.

There are no data 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 ⁽¹⁾	150 mg twice daily	450 mg twice daily
20 kg ⁽¹⁾	200 mg twice daily	600 mg twice daily
25 kg	250 mg twice daily	750 mg twice daily
From 50 kg ⁽²⁾	500 mg twice daily	1500 mg twice daily

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

⁽²⁾ 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 therapy can be initiated with either intravenous or oral administration.

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

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

4.3 Contraindications

Hypersensitivity to the active substance or other pyrrolidone derivatives or to any of the excipients.

4.4 Special warnings and precautions for use

Discontinuation

In accordance with current clinical practice, if Keppra 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).

Renal insufficiency

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

Suicide

Suicide, 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. 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 Keppra did not influence the serum concentrations of existing antiepileptic medicinal products (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these antiepileptic medicinal products did not influence the pharmacokinetics of Keppra.

As in adults, there is no evidence of clinically significant medicinal product interactions in paediatric patients receiving up to 60 mg/kg/day levetiracetam.

A retrospective assessment of pharmacokinetic interactions in children and adolescents with epilepsy (4 to 17 years) confirmed that adjunctive therapy with orally administered levetiracetam did not influence the steady-state serum concentrations of concomitantly administered carbamazepine and valproate. However, data suggested a 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. It is expected that other medicinal products excreted by active tubular secretion could also reduce the renal clearance of the metabolite. The effect of levetiracetam on probenecid was not studied and the effect of levetiracetam on other actively secreted medicinal products, *e.g.* NSAIDs, sulfonamides and methotrexate, is unknown.

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

There are no adequate data available from the use of levetiracetam in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for human is unknown. Keppra is not recommended during pregnancy and in women of childbearing potential not using contraception unless clearly necessary.

As with other antiepileptic medicinal products, physiological changes during pregnancy may affect levetiracetam concentration. Decrease in levetiracetam plasma concentrations has been observed during pregnancy. This decrease is more pronounced during the third trimester (up to 60% of baseline concentration before pregnancy). Appropriate clinical management of pregnant women treated with

levetiracetam should be ensured. Discontinuation of antiepileptic treatments may result in exacerbation of the disease which could be harmful to 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

No studies on the effects on the ability to drive and use machines have been performed. Due to possible different individual sensitivity, some patients might experience somnolence or other central nervous system related symptoms, especially at the beginning of treatment or following a dose increase. Therefore, caution is recommended in those patients when performing skilled tasks, *e.g.* driving vehicles or operating machinery. Patients are advised not to drive or use machines until it is established that their ability to perform such activities is not affected.

4.8 Undesirable effects

Summary of the safety profile

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

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

In monotherapy 49.8 % of the subjects experienced at least one drug related adverse reaction. The most frequently reported adverse reactions were fatigue and somnolence.

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

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

An increase in seizure frequency of more than 25 % was reported in 14 % of levetiracetam treated adult and paediatric patients (4 to 16 years of age) with partial onset seizures, whereas it was reported in 26 % and 21 % of placebo treated adult and paediatric patients, respectively.

When Keppra was used to treat primary generalised tonic-clonic seizures in adults and adolescents with idiopathic generalised epilepsy, there was no effect on the frequency of absences.

Tabulated list of adverse reactions

Adverse reactions reported in clinical studies (adults, adolescents and children) and from post-marketing experience are listed in the following table per System Organ Class and per frequency. For clinical trials, the frequency is defined as follows: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Data from post-marketing experience are insufficient to support an estimate of their incidence in the population to be treated.

- Infections and infestations

Common: infection, nasopharyngitis

- Blood and lymphatic system disorders

Common: thrombocytopenia

Not known: leukopenia, neutropenia, pancytopenia (with bone marrow suppression identified in some of the cases).

- Metabolism and nutrition disorders

Common: anorexia, weight increase.

Not known: weight loss

- Psychiatric disorders

Common: agitation, depression, emotional lability /mood swings, hostility/aggression, insomnia, nervousness/irritability, personality disorders, thinking abnormal.

Not known: abnormal behaviour, anger, anxiety, confusion, hallucination, psychotic disorder, suicide, suicide attempt and suicidal ideation.

- Nervous system disorders

Very common: somnolence.

Common: amnesia, ataxia, convulsion, dizziness, headache, hyperkinesia, tremor, balance disorder, disturbance in attention, memory impairment

Not known: paraesthesia, choreoathetosis, dyskinesia

- Eye disorders

Common: diplopia, vision blurred

- Ear and labyrinth disorders

Common: vertigo

- Respiratory, thoracic and mediastinal disorders

Common: cough increased

- Gastrointestinal disorders

Common: abdominal pain, diarrhoea, dyspepsia, nausea, vomiting.

Not known: pancreatitis

- Hepatobiliary disorders

Not known: hepatic failure, hepatitis, liver function test abnormal

- Skin and subcutaneous tissue disorders

Common: rash, eczema, pruritus

Not known: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme and alopecia

- Musculoskeletal and connective tissue disorders

Common: myalgia

- General disorders and administration site conditions

Very common: asthenia/fatigue.

- Injury, poisoning and procedural complications

Common: accidental injury

Description of selected adverse reactions

The risk of anorexia is higher when topiramate is coadministered with levetiracetam.

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

Paediatric population

A study conducted in paediatric patients (4 to 16 years) with partial onset seizures showed that 55.4 % of the patients in the Keppra group and 40.2 % of the patients in the placebo group experienced adverse reactions. Serious adverse reactions were experienced in none of the patients in the Keppra group and 1.0 % of the patients in the placebo group. The most commonly reported adverse reactions were somnolence, hostility, nervousness, emotional lability, agitation, anorexia, asthenia and headache in the paediatric population. Safety results in paediatric patients were consistent with the safety profile of levetiracetam in adults except for behavioural and psychiatric adverse reactions which were more common in children than in adults (38.6 % versus 18.6 %). However, the relative risk was similar in children as compared to adults.

A double-blind, placebo-controlled paediatric safety study with a non-inferiority design has assessed the cognitive and neuropsychological effects of Keppra 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 Keppra 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 Keppra 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.

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 α -ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances.

Mechanism of action

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

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

Pharmacodynamic effects

Levetiracetam induces seizure protection in a broad range of animal models of partial and primary generalised seizures without having a pro-convulsant effect. The primary metabolite is inactive. In man, an activity in both partial and generalised epilepsy conditions (epileptiform discharge/photoparoxysmal response) has confirmed the broad spectrum pharmacological profile of levetiracetam.

Clinical 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.

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

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

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

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

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

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

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

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

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

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

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

5.2 Pharmacokinetic properties

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

The intravenous administration of doses up to 4000 mg diluted in 100 ml of 0.9 % sodium chloride infused over 15 minutes and doses up to 2500 mg diluted in 100 ml of 0.9 % sodium chloride infused

over 5 minutes was evaluated. The pharmacokinetic and safety profiles did not identify any safety concerns.

Levetiracetam is a highly soluble and permeable compound. The pharmacokinetic profile is linear with low intra- and inter-subject variability. There is no modification of the clearance after repeated administration. The time independent pharmacokinetic profile of levetiracetam was also confirmed following 1500 mg intravenous infusion for 4 days with b.i.d dosing.

There is no evidence for any relevant gender, race or circadian variability. The pharmacokinetic profile is comparable in healthy volunteers and in patients with epilepsy.

Adults and adolescents

Distribution

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

No tissue distribution data are available in humans.

Neither levetiracetam nor its primary metabolite are significantly bound to plasma proteins (< 10 %). The volume of distribution of levetiracetam is approximately 0.5 to 0.7 l/kg, a value close to the total body water volume.

Biotransformation

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

Two minor metabolites were also identified. One was obtained by hydroxylation of the pyrrolidone ring (1.6 % of the dose) and the other one by opening of the pyrrolidone ring (0.9 % of the dose). Other unidentified components accounted only for 0.6 % of the dose.

No enantiomeric interconversion was evidenced *in vivo* for either levetiracetam or its primary metabolite.

In vitro, levetiracetam and its primary metabolite have been shown not to inhibit the major human liver cytochrome P₄₅₀ isoforms (CYP3A4, 2A6, 2C9, 2C19, 2D6, 2E1 and 1A2), glucuronyl transferase (UGT1A1 and UGT1A6) and epoxide hydroxylase activities. In addition, levetiracetam does not affect the *in vitro* glucuronidation of valproic acid.

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

Elimination

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

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

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

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

Elderly

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

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 carcinogenicity.

Adverse effects not observed in clinical studies but seen in the rat and to a lesser extent in the mouse at exposure levels similar to human exposure levels and with possible relevance for clinical use were

liver changes, indicating an adaptive response such as increased weight and centrilobular hypertrophy, fatty infiltration and increased liver enzymes in plasma.

No adverse effects on male or female fertility or reproduction performance were observed in rats at doses up to 1800 mg/kg/day (x 6 the MRHD on a mg/m² or exposure basis) in parents and F1 generation.

Two embryo-fetal 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 fetal 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/m² basis) and 1200 mg/kg/day for fetuses.

Four embryo-fetal 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 fetal 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/m² 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/m² 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/m² 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) with Teflon faced stoppers and sealed with an aluminium/polypropylene flip off 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 Kepra concentrate 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 Kepra concentrate

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.

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

Diluents:

- Sodium chloride (0.9%) injection
- Lactated Ringer's injection
- Dextrose 5% injection

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 September 2000

Date of last renewal: 01 September 2010

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

- B. CONDITIONS OF THE MARKETING AUTHORISATION**

A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Tablets

UCB Pharma SA Chemin du Foriest B-1420 Braine l'Alleud Belgium	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 OF THE MARKETING AUTHORISATION

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

Medicinal product subject to medical prescription.

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

Not applicable

• OTHER CONDITIONS

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 1 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the CHMP. As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR). In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMA

PSURs

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

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

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Box of 20, 30, 50, 60, 100, 200 (2 x 100)

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
200 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

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*

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

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

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

Film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

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

Medicinal product subject to medical prescription.

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, 120, 200 (2 x 100)

1. NAME OF THE MEDICINAL PRODUCT

Keppra 500 mg film-coated tablets
Levetiracetam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 500 mg levetiracetam.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

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

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

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*

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

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

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

Film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

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

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Keppra 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, 200 (2 x 100)

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

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

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

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*

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

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

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

Film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

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

Medicinal product subject to medical prescription.

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, 200 (2 x 100)

1. NAME OF THE MEDICINAL PRODUCT

Keppra 1000 mg film-coated tablets
Levetiracetam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

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

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

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*

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

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

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

Film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

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

Medicinal product subject to medical prescription.

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

Keppra 100 mg/ml oral solution
Levetiracetam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 mg levetiracetam.

3. LIST OF EXCIPIENTS

Contains E216, E218 and maltitol liquid. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

300 ml oral solution with a 10 ml syringe and an adaptor.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For children aged 4 years and above, adolescents and adults.

8. EXPIRY DATE

EXP
Do not use after 7 months of first opening the bottle.

9. SPECIAL STORAGE CONDITIONS

Store in the original container 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

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kepra 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

Keppra 100 mg/ml oral solution
Levetiracetam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 mg levetiracetam.

3. LIST OF EXCIPIENTS

Contains E216, E218 and maltitol liquid. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

150 ml oral solution with a 3 ml syringe and an adaptor.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For infants aged 6 months and above and children aged 2 to 4 years.

8. EXPIRY DATE

EXP
Do not use after 7 months of first opening the bottle.

9. SPECIAL STORAGE CONDITIONS

Store in the original container 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

Medicinal product subject to medical prescription.

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

Keppra 100 mg/ml oral solution
Levetiracetam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 mg levetiracetam.

3. LIST OF EXCIPIENTS

Contains E216, E218 and maltitol liquid. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

150 ml oral solution with a 1 ml syringe and an adaptor.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For infants aged 1 month to less than 6 months.

8. EXPIRY DATE

EXP
Do not use after 7 months of first opening the bottle.

9. SPECIAL STORAGE CONDITIONS

Store in the original container 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

Medicinal product subject to medical prescription.

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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
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

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial of 5 ml

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

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 USER

Keppra 250 mg film-coated tablets.

Levetiracetam

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

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

1. WHAT KEPPRA IS AND WHAT IT IS USED FOR

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

Keppra is used:

- on its own in patients from 16 years of age with newly diagnosed epilepsy, to treat partial onset seizures with or without secondary generalisation.
- as an add-on to other antiepileptic medicines to treat:
 - partial onset seizures with or without generalisation in patients from one month of age
 - myoclonic seizures in patients from 12 years of age with juvenile myoclonic epilepsy
 - primary generalised tonic-clonic seizures in patients from 12 years of age with idiopathic generalised epilepsy

2. BEFORE YOU TAKE KEPPRA

Do not take Keppra

- If you are allergic (hypersensitive) to levetiracetam or any of the other ingredients of Keppra.

Take special care with Keppra

- If you suffer from kidney problems, follow your doctor's instructions. He/she may decide if your dose should be adjusted.
- If you notice any slow down in the growth or unexpected puberty development of your child, please contact your doctor.
- If you notice an increase in seizure severity (e.g. increased number), 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.

Taking other medicines

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

Taking Keppra with food and drink

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

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

If you are pregnant or if you think you may be pregnant, please inform your doctor.

Keppra should not be used during pregnancy unless clearly necessary. The potential risk to your unborn child is unknown. Keppra has shown unwanted reproductive effects in animal studies at dose levels higher than you would need to control your seizures.

Breast-feeding is not recommended during treatment.

Driving and using machines

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

3. HOW TO TAKE KEPPRA

Always take Keppra exactly as your doctor has told you. You should check with your doctor 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 number of tablets following your doctor's instructions.

Monotherapy

Dose in adults and adolescents (from 16 years of age):

General dose: between 1000 mg (4 tablets) and 3,000 mg (12 tablets) 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, you must take 2 tablets in the morning and 2 tablets 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 (4 tablets) and 3,000 mg (12 tablets) each day.

Example: if your daily dose is 1,000 mg, you must take 2 tablets in the morning and 2 tablets in the evening.

Dose in infants (6 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 presentation more appropriate to infants and children under the age of 6 years.

General dose: between 20 mg per kg bodyweight and 60 mg per kg bodyweight each day.

Example: a general dose of 20 mg per kg bodyweight each day, you must give your 25 kg child 1 tablet in the morning and 1 tablet in the evening.

Dose in infants (1 month to less than 6 months):

Keppra 100 mg/ml oral solution is a presentation more appropriate to infants.

Method of administration:

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

Duration of treatment:

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

If you take more Keppra than you should:

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, as with other antiepileptic medicines, Keppra should be discontinued gradually to avoid an increase of seizures.

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

4. POSSIBLE SIDE EFFECTS

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

Tell your doctor if you have any of the following and they worry you.

Some of the side effects like sleepiness, tiredness and dizziness may be more common at the beginning of the treatment or at dose increase. These effects should however decrease over time.

The frequency of possible side effects listed below is defined using the following convention:

Very common (affects more than 1 user in 10)

Common (affects 1 to 10 users in 100)

Uncommon (affects 1 to 10 users in 1,000)

Rare (affects 1 to 10 users in 10,000)

Very rare (affects less than 1 user in 10,000)

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

Very common:

- somnolence (sleepiness);
- asthenia/fatigue (tiredness).

Common:

- infection, nasopharyngitis;
- decreased number of blood platelets;
- anorexia (loss of appetite), weight increase;
- agitation, depression, emotional instability/mood swings, hostility or aggression, insomnia, nervousness or irritability, personality disorders (behavioural problems), thinking abnormal (slow thinking, unable to concentrate);

- dizziness (sensation of unsteadiness), convulsion, headache, hyperkinesia (hyperactivity), ataxia (impaired coordinated movements), tremor (involuntary trembling), amnesia (loss of memory), balance disorder (equilibrium disorder), disturbance in attention (loss of concentration), memory impairment (forgetfulness);
- diplopia (double vision), vision blurred;
- vertigo (sensation of rotation);
- cough (increase of pre-existing cough);
- abdominal pain, nausea, dyspepsia (indigestion), diarrhoea, vomiting;
- rash, eczema, pruritus ;
- myalgia (muscle pain);
- accidental injury.

Not known:

- decreased number of red blood cells, and/or white blood cells;
- weight loss;
- abnormal behaviour, anger, anxiety, confusion, hallucination, mental disorder, suicide, suicide attempt and suicidal ideation;
- paraesthesia (tingling), difficulty in controlling movements, uncontrollable muscle spasms affecting the head, torso and limbs;
- pancreatitis, hepatic failure, hepatitis, liver function test abnormal;
- hair loss, blistering of the skin, mouth, eyes and genital area, skin eruption.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE KEPPRA

Keep out of the reach and sight of children.

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

This medicine does not require any special storage conditions.

6. FURTHER INFORMATION

What Keppra contains

The active substance is called levetiracetam. Each tablet contains 250 mg of levetiracetam.

The other ingredients are:

Tablet core: croscarmellose sodium, macrogol 6000, silica colloidal anhydrous, magnesium stearate.
Film-coating: Opadry 85F20694 (Polyvinyl alcohol-part. hydrolyzed, titanium dioxide (E171), macrogol 3350, talc, indigo carmine aluminium lake (E132)).

What Keppra looks like and contents of the pack

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

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

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder : UCB Pharma 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

Luxembourg/Luxemburg

UCB Pharma SA/NV
Tél/Tel: + 32 / (0)2 559 92 00

България

Ю СИ БИ България ЕООД
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Slovenská republika

UCB s.r.o., organizačná zložka
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Italia

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Suomi/Finland

UCB Pharma Oy Finland
Puh/Tel: + 358 10 234 6800

Κύπρος

Lifepharm (Z.A.M.) Ltd
Τηλ: + 357 22 34 74 40

Sverige

UCB Nordic A/S
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Latvija

UCB Pharma Oy Finland
Tel: + 358 10 234 6800 (Somija)

United Kingdom

UCB Pharma Ltd.
Tel : + 44 / (0)1753 534 655

Lietuva

UCB Pharma Oy Finland
Tel: + 358 10 234 6800 (Suomija)

This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>

PACKAGE LEAFLET: INFORMATION FOR THE USER

Keppra 500 mg film-coated tablets.

Levetiracetam

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

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

1. WHAT KEPPRA IS AND WHAT IT IS USED FOR

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

Keppra is used:

- on its own in patients from 16 years of age with newly diagnosed epilepsy, to treat partial onset seizures with or without secondary generalisation
- as an add-on to other antiepileptic medicines to treat:
 - partial onset seizures with or without generalisation in patients from one month of age
 - myoclonic seizures in patients from 12 years of age with juvenile myoclonic epilepsy
 - primary generalised tonic-clonic seizures in patients from 12 years of age with idiopathic generalised epilepsy

2. BEFORE YOU TAKE KEPPRA

Do not take Keppra

- If you are allergic (hypersensitive) to levetiracetam or any of the other ingredients of Keppra.

Take special care with Keppra

- If you suffer from kidney problems, follow your doctor's instructions. He/she may decide if your dose should be adjusted.
- If you notice any slow down in the growth or unexpected puberty development of your child, please contact your doctor.
- If you notice an increase in seizure severity (e.g. increased number), 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.

Taking other medicines

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

Taking Keppra with food and drink

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

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

If you are pregnant or if you think you may be pregnant, please inform your doctor.

Keppra should not be used during pregnancy unless clearly necessary. The potential risk to your unborn child is unknown. Keppra has shown unwanted reproductive effects in animal studies at dose levels higher than you would need to control your seizures.

Breast-feeding is not recommended during treatment.

Driving and using machines

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

3. HOW TO TAKE KEPPRA

Always take Keppra exactly as your doctor has told you. You should check with your doctor 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 number of tablets following your doctor's instructions.

Monotherapy

Dose in adults and adolescents (from 16 years of age):

General dose: between 1000 mg (2 tablets) and 3,000 mg (6 tablets) 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 2,000 mg, you must take 2 tablets in the morning and 2 tablets 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 (2 tablets) and 3,000 mg (6 tablets) each day.

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

Dose in infants (6 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 presentation more appropriate to infants and children under the age of 6 years.

General dose: between 20 mg per kg bodyweight and 60 mg per kg bodyweight each day.

Dose in infants (1 month to less than 6 months):

Keppra 100 mg/ml oral solution is a presentation more appropriate to infants.

Method of administration:

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

Duration of treatment:

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

If you take more Keppra than you should:

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, as with other antiepileptic medicines, Keppra should be discontinued gradually to avoid an increase of seizures.

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

4. POSSIBLE SIDE EFFECTS

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

Tell your doctor if you have any of the following and they worry you.

Some of the side effects like sleepiness, tiredness and dizziness may be more common at the beginning of the treatment or at dose increase. These effects should however decrease over time.

The frequency of possible side effects listed below is defined using the following convention:

Very common (affects more than 1 user in 10)

Common (affects 1 to 10 users in 100)

Uncommon (affects 1 to 10 users in 1,000)

Rare (affects 1 to 10 users in 10,000)

Very rare (affects less than 1 user in 10,000)

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

Very common:

- somnolence (sleepiness);
- asthenia/fatigue (tiredness).

Common:

- infection, nasopharyngitis;
- decreased number of blood platelets;
- anorexia (loss of appetite), weight increase;
- agitation, depression, emotional instability/mood swings, hostility or aggression, insomnia, nervousness or irritability, personality disorders (behavioural problems), thinking abnormal (slow thinking, unable to concentrate);
- dizziness (sensation of unsteadiness), convulsion, headache, hyperkinesia (hyperactivity), ataxia (impaired coordinated movements), tremor (involuntary trembling), amnesia (loss of memory),

- balance disorder (equilibrium disorder), disturbance in attention (loss of concentration), memory impairment (forgetfulness);
- diplopia (double vision), vision blurred;
 - vertigo (sensation of rotation);
 - cough (increase of pre-existing cough);
 - abdominal pain, nausea, dyspepsia (indigestion), diarrhoea, vomiting;
 - rash, eczema, pruritus;
 - myalgia (muscle pain);
 - accidental injury.

Not known:

- decreased number of red blood cells, and/or white blood cells;
- weight loss;
- abnormal behaviour, anger, anxiety, confusion, hallucination, mental disorder, suicide, suicide attempt and suicidal ideation;
- paraesthesia (tingling), difficulty in controlling movements, uncontrollable muscle spasms affecting the head, torso and limbs;
- pancreatitis, hepatic failure, hepatitis, liver function test abnormal;
- hair loss, blistering of the skin, mouth, eyes and genital area, skin eruption.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE KEPPRA

Keep out of the reach and sight of children.

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

This medicine does not require any special storage conditions.

6. FURTHER INFORMATION

What Keppra contains

The active substance is called levetiracetam. Each tablet contains 500 mg of levetiracetam.

The other ingredients are:

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

Film-coating: Opadry 85F32004 (Polyvinyl alcohol-part. Hydrolyzed, titanium dioxide (E171), macrogol 3350, talc, iron oxide yellow (E172)).

What Keppra looks like and contents of the pack

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

The cardboard boxes contain 10, 20, 30, 50, 60, 100, 120 and 200 film-coated tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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.

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This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>

PACKAGE LEAFLET: INFORMATION FOR THE USER

Keppra 750 mg film-coated tablets Levetiracetam

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

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

1. WHAT KEPPRA IS AND WHAT IT IS USED FOR

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

Keppra is used:

- on its own in patients from 16 years of age with newly diagnosed epilepsy, to treat partial onset seizures with or without secondary generalisation
- as an add-on to other antiepileptic medicines to treat:
 - partial onset seizures with or without generalisation in patients from one month of age
 - myoclonic seizures in patients from 12 years of age with juvenile myoclonic epilepsy
 - primary generalised tonic-clonic seizures in patients from 12 years of age with idiopathic generalised epilepsy

2. BEFORE YOU TAKE KEPPRA

Do not take Keppra

- If you are allergic (hypersensitive) to levetiracetam or any of the other ingredients of Keppra.

Take special care with Keppra

- If you suffer from kidney problems, follow your doctor's instructions. He/she may decide if your dose should be adjusted.
- If you notice any slow down in the growth or unexpected puberty development of your child, please contact your doctor.
- If you notice an increase in seizure severity (e.g. increased number), 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.

Taking other medicines

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

Taking Keppra with food and drink

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

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

If you are pregnant or if you think you may be pregnant, please inform your doctor.

Keppra should not be used during pregnancy unless clearly necessary. The potential risk to your unborn child is unknown. Keppra has shown unwanted reproductive effects in animal studies at dose levels higher than you would need to control your seizures.

Breast-feeding is not recommended during treatment.

Driving and using machines

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

Important information about some of the ingredients of Keppra

Keppra 750 mg contains Sunset Yellow FCF (E110). Sunset Yellow FCF (E110) colouring agent may cause allergic reactions.

3. HOW TO TAKE KEPPRA

Always take Keppra exactly as your doctor has told you. You should check with your doctor 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 number of tablets following your doctor's instructions.

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 3,000 mg, you must take 2 tablets in the morning and 2 tablets 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 1,500 mg, you must take one tablet in the morning and one tablet in the evening.

Dose in infants (6 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 presentation more appropriate to infants and children under the age of 6 years.

General dose: between 20 mg per kg bodyweight and 60 mg per kg bodyweight each day.

Dose in infants (1 month to less than 6 months):

Keppra 100 mg/ml oral solution is a presentation more appropriate to infants.

Method of administration:

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

Duration of treatment:

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

If you take more Keppra than you should:

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, as with other antiepileptic medicines, Keppra should be discontinued gradually to avoid an increase of seizures.

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

4. POSSIBLE SIDE EFFECTS

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

Tell your doctor if you have any of the following and they worry you.

Some of the side effects like sleepiness, tiredness and dizziness may be more common at the beginning of the treatment or at dose increase. These effects should however decrease over time.

The frequency of possible side effects listed below is defined using the following convention:

Very common (affects more than 1 user in 10)

Common (affects 1 to 10 users in 100)

Uncommon (affects 1 to 10 users in 1,000)

Rare (affects 1 to 10 users in 10,000)

Very rare (affects less than 1 user in 10,000)

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

Very common:

- somnolence (sleepiness);
- asthenia/fatigue (tiredness).

Common:

- infection, nasopharyngitis;
- decreased number of blood platelets;
- anorexia (loss of appetite), weight increase;

- agitation, depression, emotional instability/mood swings, hostility or aggression, insomnia, nervousness or irritability, personality disorders (behavioural problems), thinking abnormal (slow thinking, unable to concentrate);
- dizziness (sensation of unsteadiness), convulsion, headache, hyperkinesia (hyperactivity), ataxia (impaired coordinated movements), tremor (involuntary trembling), amnesia (loss of memory), balance disorder (equilibrium disorder), disturbance in attention (loss of concentration), memory impairment (forgetfulness);
- diplopia (double vision), vision blurred;
- vertigo (sensation of rotation);
- cough (increase of pre-existing cough);
- abdominal pain, nausea, dyspepsia (indigestion), diarrhoea, vomiting;
- rash, eczema, pruritus;
- myalgia (muscle pain);
- accidental injury.

Not known:

- decreased number of red blood cells, and/or white blood cells;
- weight loss;
- abnormal behaviour, anger, anxiety, confusion, hallucination, mental disorder, suicide, suicide attempt and suicidal ideation;
- paraesthesia (tingling), difficulty in controlling movements, uncontrollable muscle spasms affecting the head, torso and limbs;
- pancreatitis, hepatic failure, hepatitis, liver function test abnormal;
- hair loss, blistering of the skin, mouth, eyes and genital area, skin eruption.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE KEPPRA

Keep out of the reach and sight of children.

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

This medicine does not require any special storage conditions.

6. FURTHER INFORMATION

What Keppra contains

The active substance is called levetiracetam. Each tablet contains 750 mg of levetiracetam.

The other ingredients are:

Tablet core: croscarmellose sodium, macrogol 6000, silica colloidal anhydrous, magnesium stearate.
Film-coating: Opadry 85F23452 (Polyvinyl alcohol-part. hydrolyzed, titanium dioxide (E171), macrogol 3350, talc, sunset yellow FCF (E110), iron oxide red (E172)).

What Keppra looks like and contents of the pack

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

The cardboard boxes contain 20, 30, 50, 60, 80, 100 and 200 film-coated tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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Manufacturer: UCB Pharma SA, Chemin du Foriest, B-1420 Braine-l'Alleud, Belgium.
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This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>

PACKAGE LEAFLET: INFORMATION FOR THE USER

Keppra 1000 mg film-coated tablets

Levetiracetam

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

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

1. WHAT KEPPRA IS AND WHAT IT IS USED FOR

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

Keppra is used:

- on its own in patients from 16 years of age with newly diagnosed epilepsy, to treat partial onset seizures with or without secondary generalisation.
- as an add-on to other antiepileptic medicines to treat:
 - partial onset seizures with or without generalisation in patients from one month of age
 - myoclonic seizures in patients from 12 years of age with juvenile myoclonic epilepsy,
 - primary generalised tonic-clonic seizures in patients from 12 years of age with idiopathic generalised epilepsy

2. BEFORE YOU TAKE KEPPRA

Do not take Keppra

- If you are allergic (hypersensitive) to levetiracetam or any of the other ingredients of Keppra.

Take special care with Keppra

- If you suffer from kidney problems, follow your doctor's instructions. He/she may decide if your dose should be adjusted.
- If you notice any slow down in the growth or unexpected puberty development of your child, please contact your doctor.
- If you notice an increase in seizure severity (e.g. increased number), 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.

Taking other medicines

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

Taking Keppra with food and drink

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

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

If you are pregnant or if you think you may be pregnant, please inform your doctor.

Keppra should not be used during pregnancy unless clearly necessary. The potential risk to your unborn child is unknown. Keppra has shown unwanted reproductive effects in animal studies at dose levels higher than you would need to control your seizures.

Breast-feeding is not recommended during treatment.

Driving and using machines

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

3. HOW TO TAKE KEPPRA

Always take Keppra exactly as your doctor has told you. You should check with your doctor 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 number of tablets following your doctor's instructions.

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 2,000 mg, you must take 1 tablet in the morning and 1 tablet 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 2,000 mg, you must take one tablet in the morning and one tablet in the evening.

Dose in infants (6 to 23 months) in 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 presentation more appropriate to infants and children under the age of 6 years.

General dose: between 20 mg per kg bodyweight and 60 mg per kg bodyweight each day.

Dose in infants (1 month to less than 6 months):

Keppra 100 mg/ml oral solution is a presentation more appropriate to infants.

Method of administration:

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

Duration of treatment:

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

If you take more Keppra than you should:

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, as with other antiepileptic medicines, Keppra should be discontinued gradually to avoid an increase of seizures.

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

4. POSSIBLE SIDE EFFECTS

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

Tell your doctor if you have any of the following and they worry you.

Some of the side effects like sleepiness, tiredness and dizziness may be more common at the beginning of the treatment or at dose increase. These effects should however decrease over time.

The frequency of possible side effects listed below is defined using the following convention:

Very common (affects more than 1 user in 10)

Common (affects 1 to 10 users in 100)

Uncommon (affects 1 to 10 users in 1,000)

Rare (affects 1 to 10 users in 10,000)

Very rare (affects less than 1 user in 10,000)

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

Very common:

- somnolence (sleepiness);
- asthenia/fatigue (tiredness).

Common:

- infection, nasopharyngitis;
- decreased number of blood platelets.
- anorexia (loss of appetite), weight increase.
- agitation, depression, emotional instability/mood swings, hostility or aggression, insomnia, nervousness or irritability, personality disorders (behavioural problems), thinking abnormal (slow thinking, unable to concentrate);
- dizziness (sensation of unsteadiness), convulsion, headache, hyperkinesia (hyperactivity), ataxia (impaired coordinated movements), tremor (involuntary trembling), amnesia (loss of memory),

- balance disorder (equilibrium disorder), disturbance in attention (loss of concentration), memory impairment (forgetfulness);
- diplopia (double vision), vision blurred;
- vertigo (sensation of rotation);
- cough (increase of pre-existing cough);
- abdominal pain, nausea, dyspepsia (indigestion), diarrhoea, vomiting;
- rash, eczema, pruritus;
- myalgia (muscle pain);
- accidental injury.

Not known:

- decreased number of red blood cells, and/or white blood cells;
- weight loss;
- abnormal behaviour, anger, anxiety, confusion, hallucination, mental disorder, suicide, suicide attempt and suicidal ideation;
- paraesthesia (tingling), difficulty in controlling movements, uncontrollable muscle spasms affecting the head, torso and limbs;
- pancreatitis, hepatic failure, hepatitis, liver function test abnormal;
- hair loss, blistering of the skin, mouth, eyes and genital area, skin eruption.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE KEPPRA

Keep out of the reach and sight of children.

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

This medicine does not require any special storage conditions.

6. FURTHER INFORMATION

What Keppra contains

The active substance is called levetiracetam. Each tablet contains 1,000 mg of levetiracetam.

The other ingredients are:

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

Film-coating: Opadry 85F18422 (Polyvinyl alcohol-part. hydrolyzed, titanium dioxide (E171), macrogol 3350, talc).

What Keppra looks like and contents of the pack

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

The cardboard boxes contain 10, 20, 30, 50, 60, 100 and 200 film-coated tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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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.

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This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency web site:
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PACKAGE LEAFLET: INFORMATION FOR THE USER

Keppra 100 mg/ml oral solution

Levetiracetam

Read all of this leaflet carefully before you start taking this medicine.

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- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

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

1. WHAT KEPPRA IS AND WHAT IT IS USED FOR

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

Keppra is used:

- on its own in patients from 16 years of age with newly diagnosed epilepsy, to treat partial onset seizures with or without secondary generalisation
- as an add-on to other antiepileptic medicines to treat:
 - partial onset seizures with or without generalisation in patients from one month of age
 - myoclonic seizures in patients from 12 years of age with juvenile myoclonic epilepsy,
 - primary generalised tonic-clonic seizures in patients from 12 years of age with idiopathic generalised epilepsy

2. BEFORE YOU TAKE KEPPRA

Do not take Keppra

- If you are allergic (hypersensitive) to levetiracetam or any of the other ingredients of Keppra.

Take special care with Keppra

- If you suffer from kidney problems, follow your doctor's instructions. He/she may decide if your dose should be adjusted.
- If you notice any slow down in the growth or unexpected puberty development of your child, please contact your doctor.
- If you notice an increase in seizure severity (e.g. increased number), 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.

Taking other medicines

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

Taking Keppra with food and drink

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

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

If you are pregnant or if you think you may be pregnant, please inform your doctor.

Keppra should not be used during pregnancy unless clearly necessary. The potential risk to your unborn child is unknown. Keppra has shown unwanted reproductive effects in animal studies at dose levels higher than you would need to control your seizures.

Breast-feeding is not recommended during treatment.

Driving and using machines

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

Important information about some of the ingredients of Keppra

Keppra oral solution includes methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) which may cause allergic reactions (possibly delayed).

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 Keppra exactly as your doctor has told you. You should check with your doctor 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):

General dose: between 10 ml (1000 mg) and 30 ml (3,000 mg) each day, divided in 2 intakes per 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 10 ml (1,000 mg) and 30 ml (3,000 mg) each day, divided in 2 intakes per day.

Dose in infants (6 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.

General dose: between 0.2 ml (20 mg) and 0.6 ml (60 mg) per kg bodyweight each day, divided in 2 intakes per day. The exact quantity of oral solution formulation should be delivered using the syringe provided in the cardboard box.

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):

General dose: between 0.14 ml (14 mg) and 0.42 ml (42 mg) per kg bodyweight each day, divided in 2 intakes per day. The exact quantity of oral solution formulation should be delivered using the syringe provided in the cardboard box..

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:

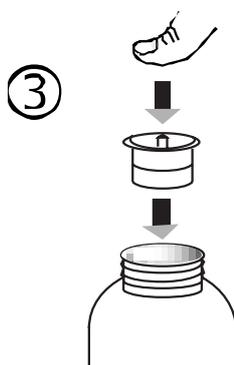
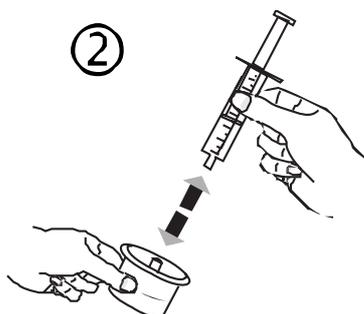
Keppra oral solution may be diluted in a glass of water or baby's bottle.

Instructions for use:

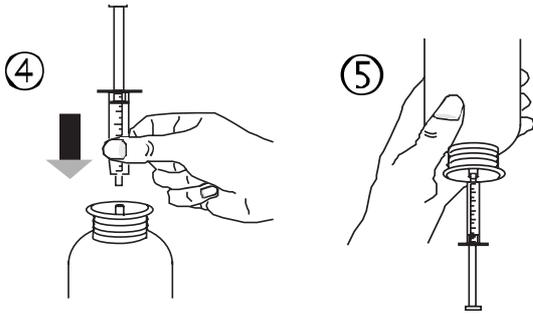
- Open the bottle: press the cap and turn it anticlockwise (figure 1)



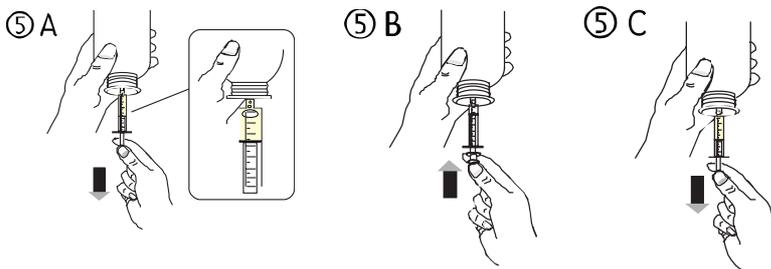
- Separate the adaptor from the syringe (figure 2). Insert the adaptor into the bottle neck (figure 3). Ensure it is well fixed.



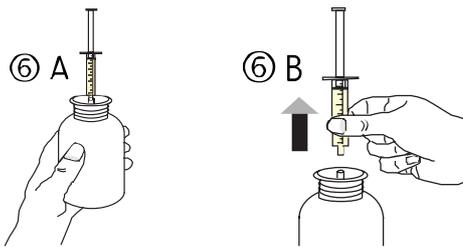
- Take the syringe and put it in the adaptor opening (figure 4). Turn the bottle upside down (figure 5).



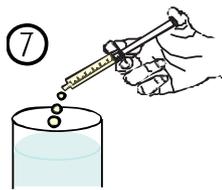
- Fill the syringe with a small amount of solution by pulling the piston down (figure 5A), then push the piston upward in order to remove any possible bubble (figure 5B). Pull the piston down to the graduation mark corresponding to the quantity in milliliters (ml) prescribed by your doctor (figure 5C).



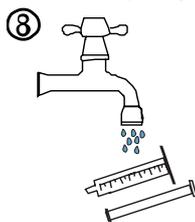
- Turn the bottle the right way up (figure 6A). Remove the syringe from the adaptor (figure 6B).



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

If you take more Keppra than you should:

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, as with other antiepileptic medicines, Keppra should be discontinued gradually to avoid an increase of seizures.

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

4. POSSIBLE SIDE EFFECTS

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

Tell your doctor if you have any of the following and they worry you.

Some of the side effects like sleepiness, tiredness and dizziness may be more common at the beginning of the treatment or at dose increase. These effects should however decrease over time.

The frequency of possible side effects listed below is defined using the following convention:

Very common (affects more than 1 user in 10)

Common (affects 1 to 10 users in 100)

Uncommon (affects 1 to 10 users in 1,000)

Rare (affects 1 to 10 users in 10,000)

Very rare (affects less than 1 user in 10,000)

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

Very common:

- somnolence (sleepiness);
- asthenia/fatigue (tiredness).

Common:

- infection, nasopharyngitis;
- decreased number of blood platelets;
- anorexia (loss of appetite), weight increase;
- agitation, depression, emotional instability/mood swings, hostility or aggression, insomnia, nervousness or irritability, personality disorders (behavioural problems), thinking abnormal (slow thinking, unable to concentrate);
- dizziness (sensation of unsteadiness), convulsion, headache, hyperkinesia (hyperactivity), ataxia (impaired coordinated movements), tremor (involuntary trembling), amnesia (loss of memory), balance disorder (equilibrium disorder), disturbance in attention (loss of concentration), memory impairment (forgetfulness);

- diplopia (double vision), vision blurred;
- vertigo (sensation of rotation);
- cough (increase of pre-existing cough);
- abdominal pain, nausea, dyspepsia (indigestion), diarrhoea, vomiting;
- rash, eczema, pruritus;
- myalgia (muscle pain);
- accidental injury.

Not known:

- decreased number of red blood cells, and/or white blood cells;
- weight loss;
- abnormal behaviour, anger, anxiety, confusion, hallucination, mental disorder, suicide, suicide attempt and suicidal ideation;
- paraesthesia (tingling), difficulty in controlling movements, uncontrollable muscle spasms affecting the head, torso and limbs;
- pancreatitis, hepatic failure, hepatitis, liver function test abnormal;
- hair loss, blistering of the skin, mouth, eyes and genital area, skin eruption.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE KEPPRA

Keep out of the reach and sight of children.

Do not use after the expiry date stated on the cardboard box and bottle after EXP:.

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

Do not use after 7 months of first opening the bottle.

Due to sensitivity to light, store in the original container.

6. FURTHER 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 aged 6 months and above and children aged 2 to 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 and Manufacturer

Marketing Authorisation Holder: UCB Pharma SA, 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.

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This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>

PACKAGE LEAFLET: INFORMATION FOR THE USER

Keppra 100 mg/ml concentrate for solution for infusion

Levetiracetam

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

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

1. WHAT KEPPRA IS AND WHAT IT IS USED FOR

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

Keppra is used:

- on its own in patients from 16 years of age with newly diagnosed epilepsy, to treat partial onset seizures with or without secondary generalisation
- as an add-on to other antiepileptic medicines to treat:
 - partial onset seizures with or without generalisation in patients from 4 years of age
 - myoclonic seizures in patients from 12 years of age with juvenile myoclonic epilepsy.
 - primary generalised tonic-clonic seizures in patients from 12 years of age with idiopathic generalised epilepsy

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

2. BEFORE YOU USE KEPPRA

Do not use Keppra

- If you are allergic (hypersensitive) to levetiracetam or any of the other ingredients of Keppra.

Take special care with Keppra

- If you suffer from kidney problems, follow your doctor's instructions. He/she may decide if your dose should be adjusted.
- If you notice any slow down in the growth or unexpected puberty development of your child, please contact your doctor.
- If you notice an increase in seizure severity (e.g. increased number), 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.

Taking other medicines

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

Using Keppra with food and drink

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

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

If you are pregnant or if you think you may be pregnant, please inform your doctor.

Keppra should not be used during pregnancy unless clearly necessary. The potential risk to your unborn child is unknown. Keppra has shown unwanted reproductive effects in animal studies at dose levels higher than you would need to control your seizures.

Breast-feeding is not recommended during treatment.

Driving and using machines

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

Important information about some of the ingredients of Keppra

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

One maximum single dose of Keppra concentrate contains 2.5 mmol (or 57 mg) of sodium. This should be taken into consideration if you are on a controlled sodium diet.

3. HOW TO USE KEPPRA

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 will 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:

- Keppra is used as a chronic treatment. You should continue Keppra treatment for as long as your doctor has told you.
- Do not stop your treatment without your doctor's advice as this could increase your seizures. Should your doctor decide to stop your Keppra treatment, he/she will instruct you about the gradual withdrawal of Keppra.
- There is no experience with administration of intravenous levetiracetam for a longer period than 4 days.

If you stop using Keppra:

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

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Keppra can cause side effects, although not everybody gets them. Tell your doctor if you have any of the following and they worry you.

Some of the side effects like sleepiness, tiredness and dizziness may be more common at the beginning of the treatment or at dose increase. These effects should however decrease over time.

The frequency of possible side effects listed below is defined using the following convention:

Very common (affects more than 1 user in 10)

Common (affects 1 to 10 users in 100)

Uncommon (affects 1 to 10 users in 1,000)

Rare (affects 1 to 10 users in 10,000)

Very rare (affects less than 1 user in 10,000)

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

Very common:

- somnolence (sleepiness);
- asthenia/fatigue (tiredness).

Common:

- infection, nasopharyngitis;
- decreased number of blood platelets;
- anorexia (loss of appetite), weight increase;
- agitation, depression, emotional instability/mood swings, hostility or aggression, insomnia, nervousness or irritability, personality disorders (behavioural problems), thinking abnormal (slow thinking, unable to concentrate);
- dizziness (sensation of unsteadiness), convulsion, headache, hyperkinesia (hyperactivity), ataxia (impaired coordinated movements), tremor (involuntary trembling), amnesia (loss of memory), balance disorder (equilibrium disorder), disturbance in attention (loss of concentration), memory impairment (forgetfulness);
- diplopia (double vision), vision blurred;
- vertigo (sensation of rotation);
- cough (increase of pre-existing cough);
- abdominal pain, nausea, dyspepsia (indigestion), diarrhoea, vomiting;
- rash, eczema, pruritus;
- myalgia (muscle pain);
- accidental injury.

Not known:

- decreased number of red blood cells, and/or white blood cells;
- weight loss;
- abnormal behaviour, anger, anxiety, confusion, hallucination, mental disorder, suicide, suicide attempt and suicidal ideation;
- paraesthesia (tingling), difficulty in controlling movements, uncontrollable muscle spasms affecting the head, torso and limbs;
- pancreatitis, hepatic failure, hepatitis, liver function test abnormal;
- hair loss, blistering of the skin, mouth, eyes and genital area, skin eruption.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE KEPPRA

Keep out of the reach and sight of children.

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

This medicine does not require any special storage conditions.

6. FURTHER INFORMATION**What Keppra contains**

The active substance is called levetiracetam. Each ml of solution for infusion 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 (Keppra concentrate) is a clear, colourless, sterile liquid. Keppra concentrate 5 ml vial is packed in a cardboard box of 10 vials.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: UCB Pharma SA, Allée de la Recherche 60, B-1070 Brussels, Belgium.

Manufacturer: UCB Pharma SA, Chemin du Foriest, B-1420 Braine-l'Alleud, Belgium
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved in

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 doctor and nurses only:

Direction for the proper use of Keppra is provided in section 3.

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

Table 1. Preparation and administration of Keppra concentrate

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.

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

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

Diluents:

- Sodium chloride (0.9%) injection
- Lactated Ringer's injection
- Dextrose 5% injection

ANNEX IV
GROUNDS FOR ONE ADDITIONAL RENEWAL

Grounds for one additional renewal

Based upon the data that have become available since the last renewal of the Marketing Authorisation, the CHMP considers that the benefit-risk balance of Keppra remains positive, but considers that its safety profile is to be closely monitored for the following reasons:

Keppra has been authorised for children from 4 years old (approved September 2005) and more recently for children from 1 month to 4 years old (approved September 2009). Due to the recent addition of these sensitive populations to the therapeutic indication, limited safety information is available in these age groups. The CHMP considers that more safety experience needs to be gained in children, and decided that the MAH should continue to submit yearly PSURs and 6-monthly specific safety reports for children < 4 years old in between yearly PSURs.

Therefore, based upon the safety profile of Keppra, which requires the submission of yearly PSURs and 6-monthly specific safety reports for children < 4 years old in between yearly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.