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LEVETIRACETAM

Keppra® Tablets, Oral Solution & Concentrate for solution for infusion

Package Insert

NAME OF THE MEDICINAL PRODUCT
Keppra® 250 mg film-coated tablet
Keppra® 500 mg film-coated tablet
Keppra® 750 mg film-coated tablet
Keppra® 1000 mg film-coated tablet
Keppra® 100 mg/ml oral solution
Keppra® 100 mg/ml Concentrate for solution for infusion

QUALITATIVE AND QUANTITATIVE COMPOSITION
Film-coated tablets:
Each film-coated tablet contains : Levetiracetam I.P. 250 mg, 500 mg, 750 mg or 1000 mg.

Oral solution:
Each ml contains : Levetiracetam I.P. 100 mg.

Concentrate for solution for infusion:
Each 5ml concentrate solution contains: Levetiracetam I.P. 500 mg.

PHARMACEUTICAL FORM
Film-coated tablet
- Levetiracetam 250 mg film-coated tablets are blue, oblong and debossed with the code ucb and 250 on one side.
- Levetiracetam 500 mg film-coated tablets are yellow, oblong and debossed with the code ucb and 500 on one side.
- Levetiracetam 750 mg film-coated tablets are orange, oblong and debossed with the code ucb and 750 on one side.
- Levetiracetam 1000 mg film-coated tablets are white, oblong and debossed with the code ucb and 1000 on one side.

Oral solution.
-Levetiracetam 100 mg/ml oral solution is a clear liquid.

Concentrate for solution for infusion
- Levetiracetam 100 mg/ml concentrate for solution for infusion is a clear, colourless, sterile solution.

CLINICAL PARTICULARS
Therapeutic indications
Levetiracetam film-coated tablets
As monotherapy:
• In the treatment of partial onset seizures with or without secondary generalization in patients from 16 years of age with newly diagnosed epilepsy.

As an adjunctive therapy:
• In myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.
• In the treatment of partial onset of seizures in adults with epilepsy.

Levetiracetam Oral Solution
As adjunctive therapy in the treatment of partial onset seizures with or without secondary generalization in adults, children and infants from 1 month of age with epilepsy.

As adjuvant therapy in treatment of partial onset seizures in adults with epilepsy when oral tablets cannot be swallowed by patients.

Levetiracetam Concentration for solution for infusion
As adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy, when oral administration is temporarily not feasible.

Posology and method of administration

Posology
By neurologists
Focal/partial onset seizures
The recommended dosing for monotherapy and adjunctive therapy is the same; as outlined below.
All indications
• Adults (≥18 years) and adolescents (12 to 17 years) weighing 50 kg or more
The initial therapeutic dose is 1000 mg/day (500 mg twice daily for both oral immediate release [tablets and oral solution] and IV formulations). This dose can be started on the first day of treatment. Depending upon the clinical response and tolerance, the daily dose can be increased up to 3000 mg/day. Dose changes can be made in 1000 mg/day increments or decrements every two to four weeks.
• Adolescents (12 to 17 years) weighing below 50 kg and children from 1 month of age
The physician should prescribe the most appropriate pharmaceutical form, presentation and strength according to weight, age and dose. Refer to Paediatric population section for dosing adjustments based on weight.

Method of administration
Levetiracetam therapy can be initiated with either intravenous or oral administration. Levetiracetam concentrate for solution for infusion is an alternative for patients when oral administration is temporarily not feasible.
Levetiracetam may be taken with or without food. After oral administration the bitter taste of Levetiracetam may be experienced.

• Oral administration
The film-coated tablets must be taken orally, swallowed with liquid. The oral solution may be taken directly or diluted in water. The daily dose is administered in two equal divided doses for the film coated tablets and the oral solution.

• Intravenous administration
Levetiracetam concentrate is for intravenous use only and the recommended dose should be diluted in at least 100 ml of a compatible diluent and administered intravenously as a 15-minute intravenous infusion.

Should a smaller volume be clinically required (e.g. paediatric population), the amount of diluent must be calculated not to exceed a levetiracetam concentration of 15 mg/ml of diluted solution and also take into consideration the total daily fluid intake of the patient.

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.

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

Special Population
Elderly population
Adjustment of the dose is recommended in elderly patients with compromised renal function (see, "Patients with renal impairment" below).

Patients with renal impairment
The Levetiracetam daily dose must be individualized according to renal function as levetiracetam clearance is related to renal function.
For children with renal impairment, this recommendation is based on a study in adult renally impaired patients.
Refer to the following tables and adjust the dose as indicated. To use the dosing tables, an estimate of the patient's creatinine clearance (CLcr) in ml/min/1.73m2 is needed.
For adults, the CLcr in ml/min may be estimated from serum creatinine (mg/dl) determination using the following formula:

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

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

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

For young adolescents, children and infants, using the following formula (Schwartz formula):

$$\text{CLcr} = \frac{\text{Height } (cm) \times \text{ks}}{\text{Serum creatinine } (mg/dl)}$$

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 adults and adolescents weighing 50 kg or more with impaired renal function

Group	Creatinine clearance (ml/min/1.73m2)	Dosage and frequency
Normal	> 80	1000 to 3000 mg/day
Mild	50-79	1000 to 2000 mg/day
Moderate	30-49	500 to 1500 mg/day
Severe	< 30	500 to 1000 mg/day
End-stage renal disease patients undergoing dialysis(1)	-	500 to 1000 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.

Dosing adjustment for infants and children patients with impaired renal function

Group	**Creatinine clearance (ml/min/1.73m2)**	**Dosage (dose for oral solution) and frequency**	
		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	10 to 20 mg/kg (0.10 to 0.20 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(1)(3)	10 to 20 mg/kg (0.10 to 0.20 ml/kg) once daily(2)(4)

(1) A 10.5 mg/kg (0.105 ml/kg) loading dose is recommended on the first day of treatment with Levetiracetam.
(2) A 15 mg/kg (0.15 ml/kg) loading dose is recommended on the first day of treatment with Levetiracetam.
(3) Following dialysis, a 3.5 to 7 mg/kg (0.035 to 0.07 ml/kg) supplemental dose is recommended.
(4) Following dialysis, a 5 to 10 mg/kg (0.05 to 0.10 ml/kg) supplemental dose is recommended.

• Patients with hepatic impairment
No dose adjustment is needed in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the creatinine clearance may underestimate the renal insufficiency. Therefore a 50 % reduction of the daily maintenance dose is recommended when the creatinine clearance is < 60 ml/min/1.73m2.

Paediatric population

• Infants 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 Levetiracetam 100 mg/ml oral solution.

Dosage recommendations for infants less than 6 months:

Weight	**Starting dose (dose for oral solution): 7 mg/kg twice daily**	**Maximum dose (dose for oral solution): 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

Infants aged 6 to 23 months, children aged 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 increments or decrements of 10 mg/kg twice daily every two weeks. The lowest effective dose should be used.

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

Dosage recommendations for children and adolescents:

Weight	**Starting dose: 10 mg/kg twice daily**	**Maximum dose: 30 mg/kg twice daily**
6 kg (1)	60 mg twice daily	180 mg twice daily
10 kg (1)	100 mg twice daily	300 mg 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 20 kg or less should preferably start the treatment with Keppra 100 mg/ml oral solution.
(2) Dosage in children and adolescents 50 kg or more is the same as in adults.

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

SPECIAL WARNINGS AND SPECIAL 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 adolescent weighing 50 kg or more: 500 mg twice daily decrements every two to four weeks; in infants older than 6 months, children and adolescents weighing less than 50 kg: dose decrease should not exceed decrements of 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).

Blood cell counts
Cases of decreased blood cell counts (neytropenia, agranulocytosis, leucopenia, thrombocytopenia and pancytopenia) have been described in association with Levetiracetam administration. Complete blood cell counts are advised in patients experiencing important weakness, pyrexia, recurrent infections or coaulation disorders (see undesirable effects).

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 Posology and method of administration section).

Suicide
Suicide, suicide attempt and suicidal ideation have been reported in patients treated with anti-epileptic agents (including levetiracetam). Patients should be advised to immediately report any symptoms of depression and/or suicidal ideation to their prescribing physician.

Psychiatric reactions and changes in behavior
Levetiracetam may cause changes in behavior (e.g. aggression, agitation, anger, anxiety, apathy, depression, hostility, and irritability) and psychotic symptoms. Patients treated with levetiracetam should be monitored for psychiatric signs and symptoms.

Seizure Worsening
A paradoxical reaction of worsening of seizure may be observed especially when starting treatment or at increase in dose.

Concentrate for solution for infusion
This medicinal product contains 0.83 mmol (or 19 mg) of sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Antiepileptic drugs
Data indicate that levetiracetam did not influence the serum concentrations of existing antiepileptic drugs (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these antiepileptic drugs did not influence the pharmacokinetics of levetiracetam

The clearance of levetiracetam was 22% higher in children taking enzyme-inducing AEDs compared to children who did not taken enzyme-inducing AEDs. Dose adjustment is not recommended. Levetiracetam had no effect on plasma concentrations of carbamazepine, valproate, topiramate, or lamotrigine.

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 drugs 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 drugs, e.g. NSAIDs, sulphonamides, and methotrexate is unknown.

Oral contraceptives and other pharmacokinetics interactions
Levetiracetam 1,000 mg daily did not influence the pharmacokinetics of oral contraceptives (ethinylestradiol and levonorgestrel); endocrine parameters (LH 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.

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

Pregnancy
A large amount of postmarketing data on pregnant women exposed to levetiracetam monotherapy (more than 1800, among which in more than 1500 exposure occurred during the 1st trimester) do not indicate increased risk of major malformations.
Limited evidence is available on the neurodevelopment of children exposed to levetiracetam monotherapy in utero. Information available from published epidemiological studies does not suggest an increased risk of neurodevelopmental disorders or delays.
Generally, therapy with multiple antiepileptic drugs (including polytherapy containing levetiracetam) is associated with a higher risk of major malformations than monotherapy (see Women of childbearing potential). Levetiracetam can be used during pregnancy if after careful assessment it is considered clinically needed. In such case, the lowest effective dose is recommended.
Physiological changes during pregnancy may affect levetiracetam concentration. A decrease in levetiracetam plasma concentrations has been observed during pregnancy. This decrease is more pronounced during the third trimester (up to 60% of baseline concentration before pregnancy).
Appropriate clinical management of pregnant women treated with levetiracetam should be ensured.

Lactation
Levetiracetam is excreted in human breast milk. Therefore, 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. No clinical data are available, potential risk for human is unknown.

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, 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.

UNDESIRABLE EFFECTS
Clinical studies
Overview
Levetiracetam has been administered to more than 3,000 subjects and patients. One thousand and twenty three (1,023) patients with epilepsy participated in controlled clinical studies. Pooled safety data from these studies conducted in adult patients showed that 46.4% and 42.2% of the patients experienced adverse reactions in the levetiracetam and placebo groups, respectively, and that 2.4% and 2.0% of the patients experienced serious adverse reactions in the levetiracetam and placebo groups, respectively.
The most commonly reported adverse reactions were somnolence, asthenia and dizziness. In the pooled safety analysis, there was no evidence of 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 adverse reaction. The most frequently reported adverse reactions were fatigue and somnolence.
A study conducted in paediatric patients (4 to 16 years) showed that 55.4% of the patients in the levetiracetam group and 40.2% of the patients in the placebo group experienced adverse reactions.
Serious adverse reactions were experienced in 0.0% of the patients in the levetiracetam 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 focal/partial onset seizures showed that 21.7 % of the patients in the levetiracetam group and 7.1% of the patients in the placebo group experienced adverse reactions. No serious adverse reactions were experienced in patients in the levetiracetam or placebo group. During the long-term follow-up study N01148, the most frequent adverse reactions in the 1m – <4y group were irritability (7.9%), convulsion (7.2%), somnolence (6.6%), psychomotor hyperactivity (3.3%), sleep disorder (3.3%), and aggression (3.3%).

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BACK

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 levetiracetam in children 4 to 16 years of age with focal/partial onset seizures. It was concluded that levetiracetam was not different (non inferior) from placebo with regard to the change from baseline of the Leiter-R Attention and Memory, Memory Screen Composite score in the per-protocol population. Results related to behavioural and emotional functioning indicated a worsening in levetiracetam treated patients on aggressive behaviour as measured in a standardized and systematic way using a validated instrument (CBCL – Achenbach Child Behavior Checklist). However, subjects, who took levetiracetam in the long-term open label follow-up study, did not experience a worsening, on average, in their behavioural and emotional functioning; in particular measures of aggressive behaviour were not worse than baseline.
A study conducted in adults and adolescents with myoclonic seizures (12 to 65 years) showed that 33.3% of the patients in the levetiracetam group and 30.0% of the patients in the placebo group experienced adverse reactions. 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 focal/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 levetiracetam group and 29.8% of the patients in the placebo group experienced adverse reactions. The most commonly reported adverse reaction was fatigue.

The most commonly reported adverse reactions with levetiracetam concentrate were headache and dizziness.

System Organ Class	Very common	Common	Uncommon	Rare
Infections and infestation	nasopharyngitis			Infection
Blood and lymphatic system disorders			Thrombocytopenia	
Metabolism and nutrition disorders		Anorexia	Weight increased	
Psychiatric disorders		Depression, hostility, aggression, insomnia, nervousness, irritability	Affect lability/mood swings, agitation	Personality disorders, thinking abnormal
Nervous system disorders	Somnolence, headache	Convulsion, balance disorder, dizziness, tremor	Amnesia memory impairment, coordination abnormal/cerebellar ataxia, disturbance in attention	Hyperkinesia
Eye disorders			Diplopia, vision blurred	
Ear and labyrinth disorders		Vertigo		
Respiratory, thoracic and mediastinal disorders		Cough		
Gastrointestinal disorders		Abnormal pain, diarrhea, dyspepsia, vomiting, nausea.		
Skin and subcutaneous tissue disorders		Rash	Eczema, pruritus	
Musculoskeletal and connective tissue disorders			Myalgia	
General disorders and administration site conditions		Asthenia/fatigue		
Injury poisoning and procedural complication			Injury	

Description of selected adverse reactions
The risk of anorexia is higher when topiramate is co administered with levetiracetam.
In several alopecia cases, recovery was observed when levetiracetam was discontinued.

Post-marketing experience
In post-marketing experience, nervous system and psychiatric disorders have been most frequently reported.
In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported in post-marketing experience. Data are insufficient to support an estimate of their incidence in the population to be treated.

System organ class	Adverse reactions
Blood and lymphatic system disorders	Pancytopenia (with bone marrow suppression identified in some of the cases), agranulocytosis, leukopenia, neutropenia
Cardiac disorders	Electrocardiogram QT prolonged
Immune system disorders	Drug reaction with eosinophilia and systemic symptoms (DRESS), anaphylactic reactions
Metabolism and nutrition disorders	Hyponatremia
Psychiatric disorders	Completed suicide, suicide attempt, suicidal ideation, psychotic disorders, abnormal behaviour, hallucination, confusional state, panic attack, anxiety, anger, delirium
Nervous system disorders	Choreoathetosis, dyskinesia, paraesthesia, lethargy, gait disturbance, seizures aggravated
Gastrointestinal disorders	Pancreatitis
Hepatobiliary disorders	Liver failure, hepatitis
Renal and urinary disorders	Acute kidney injury
Skin and subcutaneous tissue disorders	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, alopecia, Angioedema
Musculoskeletal and connective tissue disorders	Muscular weakness, rhabdomyolysis and blood creatine phosphokinase increased
Investigations	Liver function test abnormal, weight decreased

Description of selected adverse reactions
The prevalence of rhabdomyolysis and blood creatine phosphokinase increase is significantly higher in Japanese patients compared to non-Japanese patients.
Rare cases of QT prolongation have been seen in post-marketing surveillance.

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 hemodialysis. The dialyser extraction efficiency is 60 % for levetiracetam and 74 % for the primary metabolite.

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

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

In vitro studies show that levetiracetam affects intraneuronal Ca2+ levels by partial inhibition of N-type Ca2+ currents and by reducing the release of Ca2+ from intraneuronal stores. In addition it partially reverses the reductions in GABA- and glycine-gated currents induced by zinc and -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 release. 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 drug.

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

Pharmacokinetic properties
Levetiracetam is a highly soluble and permeable compound. The pharmacokinetic profile is linear and time-independent 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 (F=1) absorption, over the therapeutic dose range, levetiracetam plasma concentrations are similarly predictable following both oral or intravenous administration. 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 following oral administration (ratio of saliva/plasma concentrations ranged from 1 to 1.7 overall for oral tablet and after 4 hours post-dose for oral solution).

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

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

Metabolism
Levetiracetam is not extensively metabolised in humans. The major metabolic pathway (24 % of the dose) is an enzymatic hydrolysis of the acetamide group. Production of the primary metabolite, ucb L057, is not supported by liver cytochrome P450 isoforms. Hydrolysis of the acetamide group was measurable in a large number of tissues including blood cells. The metabolite ucb L057 is pharmacologically inactive.
Two minor metabolites were also identified. One was obtained by hydroxylation of the pyrrolidone ring (1.6 % of the dose) and the other one by opening of the pyrrolidone ring (0.9 % of the dose). Other unidentified components accounted only for 0.6 % of the dose. No enantiomeric interconversion was evidenced in vivo for neither levetiracetam nor 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 ethinylestradiol conjugation or CYP1A1/2. Levetiracetam caused mild induction of CYP2B6 and CYP3A4 at high concentrations (680 µg/mL), however at concentrations approximating to the Cmax following a repeated 1500 mg twice daily dose, the effects were not considered to be biologically relevant. Therefore, the interaction of levetiracetam with other substances, or vice versa, is unlikely.

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

The cumulative urinary excretion of levetiracetam and its primary metabolite accounted for 66 % and 24 % of the dose, respectively during the first 48 hours. The renal clearance of levetiracetam and ucb L057 is 0.6 and 4.2 ml/min/kg respectively indicating that levetiracetam is excreted by glomerular filtration with subsequent tubular reabsorption and that the primary metabolite is also excreted by active tubular secretion in addition to glomerular filtration. Levetiracetam elimination is correlated to creatinine clearance.

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

Renal impairment
The apparent body clearance of both levetiracetam and of its primary metabolite is correlated to the creatinine clearance. It is therefore recommended to adjust the maintenance daily dose of levetiracetam, based on creatinine clearance in patients with moderate and severe renal impairment.
In anuric end-stage renal disease 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 (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment, the pharmacokinetics of levetiracetam were unchanged. In subjects with severe hepatic impairment (Child-Pugh C), total body clearance was 50% that of normal subjects, but decreased renal clearance accounted for most of the decrease.
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/1.73m2.

Paediatric population
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.
Following levetiracetam 15-minute intravenous infusion at doses 14 to 20 mg/kg/day administered twice daily in patients from 1 month to 16 years of age, plasma concentrations and pharmacokinetic model derived steady-state exposure (AUC0-12) were within the range of the adult intravenous exposure as well as that observed in paediatric patients receiving equivalent doses of the oral solution.

Children (4 to 12 years)
Following single dose administration (20 mg/kg) to epileptic children, the half-life of levetiracetam was 6.0 hours. The apparent body clearance was 1.43 ml/min/kg. 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.

Preclinical safety data
Preclinical 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.

Carcinogenesis
Rats were dosed with levetiracetam in the diet for 104 weeks at doses of 50, 300 and 1800 mg/kg/day.
The highest dose corresponds to 6 times the maximum recommended daily human dose (MRHD) of 3000 mg on a mg/m2 basis and it also provided systemic exposure (AUC) approximately 6 times that achieved in humans receiving the MRHD. There was no evidence of carcinogenicity. Two studies have been conducted in mice. In one study, mice received levetiracetam in the diet for 80 weeks at doses of 60, 240 and 960 mg/kg/day (high dose is equivalent to 2 times the MRHD on a mg/m2 or exposure basis). In a second study, mice received levetiracetam by oral gavage for 2 years at dose levels of 1000, 2000 and 4000 mg/kg/day. Due to poor survival at the highest dose of 4000 mg/kg/day in this study, the high dose was reduced to 3000 mg/kg/day (equivalent to 12 times the MRHD). Neither study showed evidence of carcinogenicity
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).

PHARMACEUTICAL PARTICULARS
List of excipients
Film-coated tablets
Core
Sodium croscarmellose, Macrogol 6000, Colloidal anhydrous silica, Magnesium stearate

Coating
-250 mg film-coated tablets: Opadry 85F20694 (Polyvinyl alcohol-part.hydrolyzed, Titanium dioxide (E171), Macrogol 3350, Talc, Indigo carmine aluminium lake (E132)).
-500 mg film-coated tablets: Opadry 85F32004 (Polyvinyl alcohol-part. Hydrolyzed, Titanium dioxide (E171), Macrogol 3350, Talc, Iron oxide yellow (E172)).
-750 mg film coated tablets: Opadry 85F23452 (Polyvinyl alcohol-part. hydrolyzed, Titanium dioxide (E171), Macrogol 3350, Talc, sunset yellow FCF aluminium lake (E110), Iron oxide red (E172)).
-1000 mg film-coated tablets: Opadry 85F18422 (Polyvinyl alcohol-part. hydrolyzed, Titanium dioxide (E171), Macrogol 3350, Talc).

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

Concentrate for solution for infusion
Sodium acetate, Glacial acetic acid, Sodium chloride, Water for injections IP

Incompatibilities
The Concentrate must not be mixed with other medicinal products except compatible diluents.
It 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 (20°C to 25°C) (59-77˚F): Sodium chloride (0.9%) injection, Lactated Ringer's injection, Dextrose 5% injection.

Compatibility and Stability
Levetiracetam injection was found to be physically compatible and chemically stable when mixed with the following diluents and antiepileptic drugs for at least 24 hours and stored in polyvinyl chloride (PVC) bags at controlled room temperature 15-25°C (59-77 ˚F).
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 (person administering the medication) and would normally not be longer than 24 hours at 2 to 8°C (35-46 ˚F), unless dilution has taken place in controlled and validated aseptic conditions.

Diluents
Sodium chloride (0.9%) injection, USP
Lactated Ringer's injection
Dextrose 5% injection, USP

Other Antiepileptic Drugs
Lorazepam
Diazepam
Valproate sodium

There is no data to support the physical compatibility of levetiracetam injection with antiepileptic drugs that are not listed above.
Product with particulate matter or discoloration should not be used.

Shelf life
Film-coated tablet:-2 years.
Oral solution:-2 years
Concentrate for solution for infusion: - 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 (35-46 ˚F), unless dilution has taken place in controlled and validated aseptic conditions.

Storage
Film-coated tablet: Store protected from moisture & light, at a temperature not exceeding 30˚C
Oral solution: Store protected from moisture & light, at a temperature not exceeding 30˚C.
Concentrate for solution for infusion : Store at controlled room temperature (20°C to 25°**C).**
Protect from light & moisture. Do not freeze.

Nature and contents of container:
Keppra® 250 mg film-coated tablets are packaged in strips containing 10 tablets placed into a monocarton.
Keppra® 500 mg film-coated tablets are packaged in strips containing 10 tablets placed into a monocarton.
Keppra® 750 mg film-coated tablets are packaged in strips containing 10 tablets placed into a monocarton.
Keppra® 1000 mg film-coated tablets are packaged in strips containing 10 tablets placed into a monocarton.
Keppra® 100 mg/ml oral solution is supplied as 100 ml bottles.
Keppra® 100 mg/ml concentrate for solution for infusion is packed in glass vials (type I) with rubber stoppers and sealed with an aluminium/polypropylene flip off cap. The vials are placed into cartons of 10 vials. Each single use vial contains 5 ml of concentrate.

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Telangana, INDIA.

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Keppra® 250 mg film-coated tablet
Keppra® 500 mg film-coated tablet
Keppra® 750 mg film-coated tablet
Keppra® 1000 mg film-coated tablet
Manufactured in India by:
Pure & Cure Healthcare Pvt. Ltd.
(A subsidiary of
Akums Drugs & Pharmaceuticals Ltd.)
Plot No. 26A, 27-30, Sector-8A, I.I.E., SIDCUL,
Ranipur, Haridwar-249403, Uttarakhand.

Keppra® 100 mg/ml oral solution
Manufactured in India by:
Akums Drugs & Pharmaceuticals Ltd.
Plot No. 22, Sector 6-A, IIE, SIDCUL,
Ranipur, Haridwar-249403,
Uttarakhand, India.

Keppra® 100 mg/ml Concentrate for solution for infusion
Manufactured in India by:
Akums Drugs & Pharmaceuticals Ltd.
Plot No. 2,3,4 & 5, Sector 6B, I.I.E.,
SIDCUL, Ranipur, Haridwar - 249 403.

350 MM

240 MM