

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LEV-END[®] 1000 mg film coated tablet.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:

Each film coated tablet contains 1000 mg levetiracetam.

Excipient(s):

Crosscarmellos sodium 34 mg

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet.

White, oval biconvex film coated tablets, "L1000" logo and score on one side.

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

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalization in adults and children 4 year-old and over of age with epilepsy.
- Indicated as adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents 12 years old and older with Juvenile Myoclonic Epilepsy.
- Indicated as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and adolescents 12 years old and older with idiopathic generalized epilepsy.
- Indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalization in patients 16 years old and older with epilepsy.

4.2. Posology and method of administration

Posology / frequency and duration of administration

The daily dose is administered in two equally divided doses.

- 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 2 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 (12-17 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 1500 mg twice daily. Dose changes can be made in 500 mg twice daily increases or decreases every 2- 4 weeks.

For children aged from 4 to 11 and adolescents (12-17 years) weighing less than 50kg

In infants and children aged under 4 years should be used LEV-END® 100 mg/ml oral solution. 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 2 weeks. The lowest effective dose should be used.

Dosage in children 50 kg or greater is the same as in adults. For all indications, see section Adults (≥18 years) and adolescents (12-17 years) weighing 50 kg or more above.

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

Dose recommendations for children and adolescents

Weight	Starting dose: 10 mg/kg twice daily	Maximum dose: 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 weighing 25 kg or less are recommended to start the treatment with LEV-END® 100 mg/ml Oral Solution.

(2) Dose in children and adolescents weighing 50 kg or more is the same as in adults.

Discontinuation of treatment

In accordance with current clinical experience, the recommendation is to discontinue LEV-END® treatment with a gradual dose reduction (e.g. in adults and adolescents weighing more than 50 kg, by reducing the dose by 2 x 500 mg/day every 2 to 4 weeks; in children and adolescents weighing less than 50 kg, by reducing the dose by 2 x 10 mg/kg/day every 2 weeks).

Method of administration

The film-coated tablets must be taken orally, swallowed with a sufficient quantity of liquid. They may be taken with or without food. After oral administration the bitter taste of levetiracetam may be experienced.

Additional information on special populations

Renal/Hepatic impairment:

The daily dose must be individualized according to renal function. For adult patients, the following table is used and the dose is adjusted as indicated in the table. To use this dosing table, the patient's creatinine clearance (CL_{Cr}) must be estimated in ml/min.

The CL_{Cr} in ml/min value is estimated from serum creatinine (mg/dl) determination for adults and adolescents weighing 50 kg or more 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:

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

Dosing adjustment for adult and adolescents over 50 kg patients with impaired renal function:

Group	Creatinine clearance (ml/min/1.73m ²)	Dosage and frequency
Normal	> 80	500-1500 mg twice daily
Mild	50-79	500-1000 mg twice daily
Moderate	30-49	250-750 mg twice daily
Severe	< 30	250-500 mg twice daily
End-stage renal disease patients undergoing dialysis ⁽¹⁾	-	500-1000 mg once daily ⁽²⁾

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

(2) Following dialysis, a 250-500 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= 0.55 in children less than 13 years and adolescent female;

ks= 0.7 in adolescent male

Dosing adjustment for children and under 50 kg adolescent patients with impaired renal function

Group	Creatinine clearance (ml/min/1.73m ²)	Dosage frequency ¹
		Children over 4 years and adolescents less than 50 kg
Normal	≥ 80	10-30 mg/kg (0.10-0.30 ml/kg) twice daily
Mild	50-79	10-20 mg/kg (0.10-0.20 ml/kg) twice daily
Moderate	30-49	5-15 mg/kg (0.05-0.15 ml/kg) twice daily
Severe	< 30	5-10 mg/kg (0.05-0.10 ml/kg) twice daily
Terminal renal impairment and patients undergoing dialysis	-	10-20 mg/kg (0.10-0.20 ml/kg) once daily ⁽²⁾⁽³⁾

- (1) For the patients have tablet swallowing problem and administered under 250 mg dose; should be used LEV-END® 100 mg/ml oral solution.
- (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 5-10 mg/kg (0.05 to 0.10 ml/kg) supplemental dose is recommended.

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 $< 60 \text{ ml/min/1.73 m}^2$

Pediatric population:

LEV-END® film-coated tablets are not recommended for use in children under the age of 4 years. LEV-END® oral solution is the presentation to use in children under the age of 4 years. In addition, because of the efficacy of dosage should not be used in children under 25 kg weighted with onset therapy and have swallowing problem and also administration under 250mg dose. For all these patients, should be used LEV-END® oral solution.

The effectiveness and safety of LEV-END as a monotherapy treatment in children and adolescents under 16 years of age has not been proven.

Children and adolescents aged 16 years should not used in monotherapy.

Geriatric population:

Adjustment of the dose is recommended in elderly patients (65 years and older) with compromised renal function (see section 4.2 Posology and method of administration, Renal/Hepatic impairment).

4.3 Contraindications

Levetiracetam is contraindicated in patients with hypersensitivity to other pyrrolidone derivatives or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions

Acute kidney injury

Very rarely acute kidney injury has been associated with levetiracetam use, and the start time varies from a few days to several months.

Renal impairment:

Patients with renal impairment may require dose adjustment. Therefore in patients with severely impaired hepatic function, assessment of renal function is recommended before dose selection (*see section 4.2 Posology and method of administration*).

Blood cell counts

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

Suicide:

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

Therefore patients should be monitored closely for signs of depression and/or suicidal

ideation and behaviors 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 behavior emerge.

Unusual and aggressive behaviour:

Levetiracetam may cause psychotic symptoms and behavioural abnormalities such as irritability and aggression. Patients treated with levetiracetam should be monitored for developing psychiatric symptoms involving significant mood and/or personality changes. If such behaviour is noticed, adjustment of treatment accordingly or gradual discontinuation of the drug should be considered. If discontinuation of the drug is considered, section 4.2 should be consulted.

Worsening of seizures:

As with other types of antiepileptic drugs, levetiracetam may rarely exacerbate seizure frequency or severity. This paradoxical effect has most often been reported within the first month of starting or increasing the dose of levetiracetam and has been reversible upon discontinuation or dose reduction. Patients should be advised to consult their doctor immediately in case of exacerbation of epilepsy. For example, lack of efficacy or seizure worsening has been reported in patients with epilepsy associated with voltage-gated sodium channel alpha subunit 8 (SCN8A) mutations.

Electrocardiogram QT interval prolongation:

Rare cases of ECG QT interval prolongation were observed during post-marketing monitoring. Levetiracetam should be used with caution in patients with QTc interval prolongation, concomitant treatment with drugs that affect the QTc interval, or in patients with pre-existing cardiac disease or electrolyte disturbances.

Pediatric population:

LEV-END[®] tablet formulation population should not be used in children under aged 4 years.

According to current data related to children, there is no effect on adolescence and growth. However, long term effects are not known on the learning, intelligence, growth, endocrine functions, adolescence and child-bearing potential in children.

The efficacy and confidence of levetiracetam has not evaluated in infants under 1 year-old, detailly. In the clinical trials, 35 infants under 1 year of age were included, only 13 infants were 6 months old.

LEV-END[®] tablet contains less than 1 mmol (23 mg) of sodium per dose; it is "sodium free".

4.5 Interaction with other medicinal products and other forms of interaction

Antiepileptic medicinal preparations:

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

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

A retrospective assessment of pharmacokinetic interactions in children and adolescents (4 to 17 years) with epilepsy confirmed that adjunctive therapy with orally administered levetiracetam did not influence the steady-state serum concentrations of concomitantly administered

carbamazepine and valproate. However, data suggested a 20 % higher levetiracetam clearance in children taking enzyme-inducing antiepileptic medicinal products. Dose adjustment is not required.

Probenecid

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

Methotrexate

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

Oral contraceptives and other pharmacokinetic interactions:

Levetiracetam 1000 mg daily did not change the pharmacokinetics of oral contraceptives (ethinyl- estradiol, levonorgestrel) and endocrine parameters (luteinizing hormone and progesterone).

Levetiracetam 2000 mg daily did not influence the pharmacokinetics of digoxin and warfarin; prothrombin times were not modified. Co-administration with digoxin, oral contraceptives and warfarin did not influence the pharmacokinetics of levetiracetam.

Laxatives:

There are reports of decreased efficacy of levetiracetam in the use of osmotic laxative macrogol concomitantly with oral levetiracetam. For this reason, macrogol should not be taken orally before 1 hour and after 1 hour in use of levetiracetam.

Food and alcohol:

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

Additional information on special populations:

Pediatric population:

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

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4.6 Pregnancy and lactation General advice

Pregnancy category: C

Women of childbearing potential/Birth control (Contraception)

LEV-END[®] is not recommend for women who have potential for childbearing and who do not control birth control; unless it is clinically necessary.

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

Pregnancy

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 suggest an increase in the risk for major congenital malformations. Only limited evidence is available on the neurodevelopment of children exposed to Keppra monotherapy in utero. However, current epidemiological studies (on about 100 children) do not suggest an increased risk of neurodevelopmental disorders or delays.

Treatment with multiple antiepileptic drugs is associated with a higher risk of congenital malformation than with monotherapy, and monotherapy should be considered accordingly.

Studies in animals have shown reproductive toxicity (*see section 5.3 Preclinical safety data*).

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

Lactation

Levetiracetam is excreted in human breast milk. Therefore, breast-feeding is not recommended during treatment with LEV-END[®]. However, the benefits of breastfeeding to the child and the benefits of LEV-END[®] treatment to the mother should be considered when deciding whether breastfeeding is to be discontinued or whether LEV-END[®] treatment is to be discontinued/avoided.

Reproductive ability/Fertility

Animal studies were shown that no adverse effects on male or female fertility or reproduction performance. (*see 5.3.Preclinical safety data*) There are no clinical data available, and the potential risks to humans are unknown.

4.7 Effects on ability to drive and use machines

No studies have been performed on the effects on activities that require alertness such as driving and using machines. Therefore, due to possible different individual sensitivity, somnolence or other central nervous system related symptoms may occur, 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 Safety profile

The most commonly reported adverse reactions are nasopharyngitis, somnolence, headache,

weakness and dizziness. The following profile of adverse effects is based on an analysis of combined placebo-controlled clinical trials with a total of 3416 patients treated with levetiracetam and all the indications reviewed. This data is supported by the use of levetiracetam in postmarketing experience as well as related open label extension studies. The safety profile of levetiracetam is generally similar between age groups (adult and pediatric patients) and approved epilepsy indications.

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Undesirable effects reported in clinical studies (adults, adolescents, children and infants >1 month) or from post-marketing experience are listed in the following table per system organ class and per frequency. Very common ($\geq 1/10$); common ($\geq 1/100$, $<1/10$); uncommon ($\geq 1/1,000$, $<1/100$); rare ($\geq 1/10,000$, $<1/1,000$); very rare ($<1/10,000$), including isolated reports. Data from post-marketing experience are insufficient to support an estimate of their incidence in the population to be treated.

Infections and infestations

Very common: nasopharyngitis

Common: infection

Blood and lymphatic system disorders

Uncommon: thrombocytopenia, leucopenia

Rare: neutropenia, pancytopenia, agranulocytosis

Immun system disorders

Rare: eosinophil and drug reactions with systemic symptom (DRESS), hypersensitivity (including angioedema and anaphylaxis)

Metabolism and nutrition disorders

Common: anorexia

Uncommon: weight loss, weight gain

Rare: hyponatremia

Psychiatric disorders

Common: depression, hostility/aggression, anxiety, insomnia, nervousness/irritability

Uncommon: suicide, suicide attempt and suicidal ideation, psychotic disorder, abnormal behavior, hallucination, anger, confusion, panic attack, emotional lability/mood swings, agitation

Rare: suicide, personal abnormality, abnormal thoughts.

Very rare: obsessive-compulsive disorder**

Nervous system disorders

Very common: somnolence, headache

Common: convulsion, balance disorder, dizziness, tremor, lethargy.

Uncommon: amnesia, memory impairment, coordination abnormality/ataxia, paraesthesia, attention deficit,

Rare: Chorea/athetosis, dyskinesia, hyperkinesia, gait disturbance, encephalopathy, seizure exacerbation, neuroleptic malignant syndrome*

Eye disorders

Uncommon: diplopia, blurred vision

Ear and labyrinth disorders

Common: vertigo

Cardiac disorders

Rare: electrocardiogram QT prolongation

Respiratory, thoracic and mediastinal disorders

Common: cough

Gastrointestinal disorders

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

Rare: pancreatitis

Hepatobiliary disorders

Uncommon: abnormal liver function tests

Rare: hepatic failure, hepatitis

Renal and Urinary Disorders

Rare: acute kidney injury

Skin and subcutaneous tissue disorders

Common: rash

Uncommon: alopecia, eczema, pruritus

Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme

Musculoskeletal disorders, connective tissue and bone diseases

Common: muscle weakness, muscle pain (myalgia)

Rare: Rhabdomyolysis and blood creatine phosphokinase increased*

General disorders and administration site conditions

Very common: asthenia/fatigue

Injury, poisoning and procedural complications

Uncommon: accidental injury

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

** In post-marketing follow-up, it was observed that obsessive-compulsive disorders developed very rarely in patients with a history of underlying obsessive-compulsive disorder (OCD) or psychiatric disorder.

Describing adverse reaction

If topiramate is administered with levetiracetam, the risk of anorexia is higher. In various alopecia cases, improvement was observed when levetiracetam treatment was terminated. Bone marrow suppression was detected in some cases of pancytopenia.

Cases of encephalopathy were usually seen at the beginning of treatment (several days to several months) and resolved after discontinuation of treatment.

Pediatric population

In patients aged 1 month to less than 4 years, a total of 190 patients have been treated with levetiracetam in placebo-controlled and open label extension studies. Sixty of these patients

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

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

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

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

Reporting of suspected adverse reactions

Reporting of suspected adverse drug reactions after marketing authorisation is of great importance. Reporting allows the benefit/risk balance of the medicinal product to be continuously monitored. Healthcare professionals are required to report any suspected adverse reactions to the Turkish Pharmacovigilance Centre (TÜFAM) (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; tel: 0 800 314 00 08; fax: 0 312 218 35 99).

4.9 Overdose and its management

Symptoms

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

Management

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 should be symptomatic and may include hemodialysis. The dialyzer 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) and chemically unrelated to existing antiepileptic drugs.

Mechanism of action

The mechanism of action of levetiracetam still could not completely explained. 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 has been shown to induce seizure protection in a broad range of animal models of partial and primary generalized seizures without having a pro-convulsant effect. The primary metabolite is inactive. In human, an activity in both partial and generalized 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 generalization in adults, adolescents, children 4 year of age and elder 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.

Pediatric population

In pediatric patients (4-16 years of age), levetiracetam efficacy was established in a double-blind, placebo-controlled study with a duration of 14 weeks, which included 198 patients. 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.

The efficacy of levetiracetam in paediatric patients (aged 1 month to less than 4 years) was determined in a double-blind placebo-controlled study in which 116 patients were included and the duration of treatment was 5 days. In this study, patients were prescribed a daily oral solution dose of 20 mg/kg, 25 mg/kg, 40 mg/kg or 50 mg/kg based on age titration schedules. In this study, a dose of

20 mg/kg/day titrated up to 40 mg/kg/day was used in infants aged 1 month to less than 6 months and a dose of 25 mg/kg/day titrated up to 50 mg/kg/day was used in infants and children aged 6 months to less than 4 years. The total daily dose was administered twice daily.

The primary measure of efficacy was 48-hour video EEG using a blinded centre reader is the proportion of patients who responded (the percentage of patients who showed a $\geq 50\%$ reduction from baseline in the average daily frequency of partial-onset seizures). The efficacy analysis included 109 patients with at least 24 hours of video EEG at both baseline and evaluation periods. 43.6% of patients treated with levetiracetam and 19.6% of patients receiving placebo were considered responders. The results are consistent across the age group. During ongoing long-term treatment, 8.6% of patients spent at least 6 months and 7.8% at least 1 year seizure-free.

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

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

Efficacy of levetiracetam as monotherapy was established in a double-blind, parallel group, noninferiority 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, and 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 generalized tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalized 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

General properties

The pharmacokinetic profile of levetiracetam, a highly soluble and permeable compound, 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 is seen in adults and children (ratio of saliva/plasma concentrations ranges from 1 to 1.7 for oral tablet formulation and after 4 hours post-dose for oral solution formulation).

Absorption

Levetiracetam is rapidly absorbed after oral administration, and 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}) detected following a single 1000 mg dose and a total 1000 mg dose administered twice daily are 31 and 43 µg/ml, respectively. The extent of absorption is dose-independent and is not affected by food.

Distribution

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

Biotransformation

Levetiracetam is not extensively metabolized in humans. The major metabolic pathway (24% of the dose) is an enzymatic hydrolysis of the acetamide group. Liver cytochrome P₄₅₀ isoforms are not involved in the production of the primary metabolite, ucb L057. 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 levetiracetam with other drugs, or other drugs with levetiracetam is not expected.

Elimination

The plasma half-life in adults is 7 ± 1 hours and does not vary either with dose, route of administration or repeated administration. The mean total body clearance is 0.96 ml/min/kg. A mean 95% of the dose administered is excreted from the body via urine (approximately 93% of the dose is excreted within 48 hours). Only 0.3% of the dose is excreted via feces.

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. This indicates 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.

Characteristic in patients

Renal/hepatic impairment

The 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 (*see section 4.2 Posology and method of administration*).

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

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

Pediatric population

Children(4-12 years old)

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

Following repeated oral dose administration of 20 to 60 mg/kg/day to epileptic children 4-12 years of age, levetiracetam was rapidly absorbed from gastrointestinal tract. 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 body clearance was 1.1 ml/min/kg.

Geriatric population

In the elderly, the half-life is increased by about 40% (10-11 hours) due to the decrease in renal function in this population (*see section 4.2 Posology and method of administration*).

5.3 Preclinical safety data

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

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

In studies conducted in rats, no adverse effects on male or female fertility or reproductive performance were observed in either parent or F1 puppies at doses of 1800 mg / kg / day (6 times the maximum recommended dose in humans on a mg/m^2 basis)

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 embryo mortality and no increased incidence of malformations. The NOAEL (No Observed Adverse Effect Level) was 3600 mg/kg/day for pregnant female rats (12 times the maximum recommended human dose on a mg/m^2 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. This was associated with increased incidence of fetuses with cardiovascular/skeletal anomalies. The NOAEL was <200 mg/kg/day for the female and 200 mg/kg/day for the fetuses (equal to the maximum recommended human dose on a mg/m^2 basis).

Oral administration of levetiracetam to pregnant rabbits during the organogenesis period, resulted an increase in embryo-fetal mortality and fetal skeletal abnormalities at 600 mg / kg / day doses (4 times MRHD on mg / m^2 basis) and; a decrease in fetal weights and an increase in the incidence of fetal malformations at a dose of 1800 mg / kg / day (12 times MRHD in mg / m^2). The dose without a developmental effect is 200 mg / kg / day (equivalent to MRHD in mg / m^2). Maternal toxicity was also observed as 1800mg / kg / day.

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 (6 times the maximum recommended human dose on a mg/m^2 basis).

Neonatal and juvenile animal studies in rats and dogs demonstrated that there were no adverse effects seen in any of the standard developmental or maturation endpoints at doses up to 1800 mg/kg/day (6-17 times the maximum recommended human dose on a mg/m^2 basis)

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

PEG 6000

Colloidal anhydr silica
Magnesium stearate
Croscarmellose sodium
Hydroxypropyl methylcellulose
Talc
Titanium dioxide

6.2. Incompatibilities

There are not any known incompatibility.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Keep at room temperature below 25°C.

6.5. Nature and contents of container

In PVC-PE-PVDC/Al foil blister package, 50 Film Coated Tablets, package leaflet, cardboard boxes.

6.6 Disposal of waste materials derived from medicinal product and other special precautions

Disposal of unused medicinal products or waste materials derived from the used medicinal product should conduct according to the "Regulation of Medicinal Waste Control" and "Regulation of Packaging and Packaging Waste Control"

7. MARKETING AUTHORISATION HOLDER

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Okmeydanı, Boruçiçeği Sok. No:16
34382 Şişli – İSTANBUL
0212 220 64 00
0212 222 57 59

8. MARKETING AUTHORISATION NUMBER(S)

217/14

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31.11.2008

Renewal of the authorisation: 18.09.2014

10. DATE OF REVISION OF THE SmPC

25.01.2024