

SUMMARY OF PRODUCT CHARACTERISTIC

1. NAME OF THE MEDICINAL PRODUCT

LEV-END® 100 mg/ml oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:

Per ml:

Levetiracetam	100 mg
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Excipient:

1 ml solution;

Methylhydroxybenzoate (E218)	1.4 mg
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Propylhydroxybenzoate (E216)	0.14 mg
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Maltitol solution (E965)	400 mg
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Glycerol	200 mg
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Sodium citrate dihydrate	10 mg
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See 6.1 for excipients.

3. PHARMACEUTICAL FORM

Oral solution

Almost colorless, clear solution with characteristic odor.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- In elderly adult patients with swallowing difficulties and in babies and children;
- In children over 1 month of age and adults with partial onset seizures with or without secondary generalization as adjunctive therapy,
- Myoclonic in adolescents and adults over 12 years of age with Juvenile Myoclonic Epilepsy as an additional treatment for seizures,
- Primary in children and adults aged 12 years and older with idiopathic generalized epilepsy as adjunctive therapy in generalized tonic-clonic seizures,

- In patients aged 16 years and older, partial onset with or without secondary generalized used as monotherapy in the treatment of seizures.

4.2 Posology and method of administration

Posology/Frequency and duration of administration:

The total daily dose should be given in two equal doses.

- Monotherapy

In adults and adolescents over 16 years of age

The recommended starting dose is the same as for add-on therapy (see below).

Additional treatment

Adults (≥ 18 years) and adolescents (12-17 years) weighing 50 kg or more

The initial treatment dose is 500 mg twice daily. This dose can be started from the first day of treatment. However, the physician may prescribe a lower initial dose of 250 mg twice daily, based on the evaluation of the reduction in seizures against potential adverse effects. This dose may be increased to 500 mg twice daily after two weeks.

Depending on clinical response and tolerability, the dose may be increased up to 1500 mg twice daily. Dose changes may be increased or decreased every 2 to 4 weeks to 250 mg or 500 mg twice daily.

Babies aged 6-23 months, children aged 2-11 years and adolescents weighing less than 50 kg (12-17 age)

The initial treatment dose is 10 mg/kg twice daily. Based on clinical response and tolerability, the dose may be increased to 30 mg/kg twice daily in increments of 10 mg/kg twice daily every two weeks. Dose changes may be increased or decreased every 2 weeks, not exceeding 10 mg/kg twice daily. The lowest effective dose should be used for all indications.

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

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

Recommended dosage for babies over 6 months of age, children and adolescents:

Weight	Starting dose: 10 mg/kg twice a day	Maximum dose: 30 mg/kg twice a day
6 kg ⁽¹⁾	60 mg twice a day (0,6ml)	180 mg twice a day (1,8ml)
10 kg ⁽¹⁾	100 mg twice a day (1 ml)	300 mg twice a day (3 ml)
15 kg ⁽¹⁾	150 mg twice a day (1,5ml)	450 mg twice a day (4,5ml)
20 kg ⁽¹⁾	200 mg twice a day (2ml)	600 mg twice a day (6ml)
25 kg	250 mg twice a day (2,5ml)	750 mg twice a day (7,5 ml)
Over 50 kg ⁽²⁾	500 mg twice a day (5ml)	1500 mg twice a day (15ml)

(1) Children weighing 25 kg or less are recommended to start treatment with LEV-END® 100 mg/ml Oral Solution.

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

Babies between 1-6 months

The starting treatment dose is 7 mg/kg twice daily. Depending on clinical response and tolerability, the dose may be increased to the recommended dose of 21 mg/kg twice daily in increments of 7 mg/kg twice daily every two weeks. Dose changes may be increased or decreased every 2 weeks, not exceeding 7 mg/kg twice daily. The lowest effective dose should be used.

Infants should start treatment with LEV-END® 100mg/ml oral solution.

Recommended dosage for *Babies between 1-6 months*:

Weight	Starting dose: 7 mg/kg twice a day mg	Maximum dose: 21 mg/kg twice a day mg
4 kg	28 mg twice a day mg (0,3ml)	84 mg twice a day mg (0,85ml)
5 kg	35 mg twice a day mg (0,35 ml)	105 mg twice a day mg (1,05 ml)
7 kg	49 mg twice a day mg (0,5ml)	147 mg twice a day mg (1,5ml)

The doctor should prescribe the most appropriate pharmaceutical form, route of administration and strength according to weight and dose.

One form of presentation is available:

- A 10ml oral syringe (which can hold up to 1000 mg levetiracetam) graduated every 0.25ml (corresponding to 25 mg) and a 300 ml bottle.

Discontinuation of treatment

The recommendation in accordance with current clinical experience 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 and babies over 6 months, by reducing the dose by no more than 2 x 10 mg/kg/day every 2 weeks; in babies under 6 months, by reducing the dose by no more than 2 x 7 mg/kg/day every 2 weeks).

Method of administration:

The oral solution is diluted in a glass of water or a bottle and taken orally with or without meals. After oral administration, levetiracetam may leave a bitter taste. The measuring pipette and instructions for use are in the LEV-END® box.

Additional information for special populations:**Renal/liver impairment:**

The daily dose is individualized according to renal function. The following table is used for adult patients and dose adjustment is made as indicated in the table. To use this dose table, the patient's creatinine clearance (CLcr) must be calculated in ml/min. For adults 50 kg and over and adolescents, CLcr ml/min is calculated by substituting the serum creatinine (mg/dl) value into the formula below.

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

CLcr is then set for Body Surface Area (BSA) as indicated below:

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

Dose adjustment in adults with impaired renal function and adolescents over 50 kg

Group	Creatinine Clearance (ml/min/1,73 m ²)	Dose and Dose Frequency
Normal	≥ 80	500-1500 mg twice a day
Mild	50 - 79	500-1000 mg twice a day
Moderate	30 - 49	250-750 mg twice a day
Severe	< 30	250-500 mg twice a day
In patients with end-stage renal failure and on dialysis ⁽¹⁾	-	500-1000 mg once a day ⁽²⁾

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

(2) Following dialysis, an additional dose of 250 - 500 mg is recommended.

Since levetiracetam clearance is related to renal function, the dose of levetiracetam should be adjusted according to renal function in children with renal impairment. This recommendation is based on a study in adult patients with renal impairment.

CLcr in ml/min/1.73m²; the following formula for young adolescents, children and infants (Schwartz formula) can be estimated from the determination of serum creatinine (mg/dl):

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

ks= 0.45 for infants up to 1 year of age; ks= 0.55 for children under 13 years of age and adolescents in females; ks= 0.7 in adolescent males.

Dose adjustment for babies, children and adolescents weighing less than 50 kg with impaired renal function

Group	Creatinin Clearance (ml/min/1,73m ²)	Dose and Dose Frequency ⁽¹⁾	
		Babies aged 1-6 months	Babies aged 6-23 months, children and adolescents over 50kg
Normal	≥ 80	7-21mg/kg twice a day (0,07-0,21ml/kg)	10-30mg/kg twice a day (0,10-0,30ml/kg)
Mild	50 - 79	7-14mg/kg twice a day (0,07-0,14ml/kg)	10-20mg/kg twice a day (0,10-0,20ml/kg)
Moderate	30 - 49	3,5-10,5mg/kg twice a day (0,035-0,105ml/kg)	5-15mg/kg twice a day (0,05-0,15ml/kg)
Severe	< 30	3,5-7mg/kg twice a day (0,035-0,07ml/kg)	5-10mg/kg twice a day (0,05-0,10ml/kg)
In patients with end-stage renal failure and on dialysis	-	7-14mg/kg once a day (0,07-0,14ml/kg) ^{(2) (4)}	10-20mg/kg once a day (0,10-0,20 ml/kg) ^{(3) (5)}

(1) LEV-END® oral solution should be used for patients with difficulty swallowing tablets and for dosing below 250 mg and for dosing not in multiples of 250 mg if the recommended dose cannot be achieved by taking more than one tablet.

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

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

(4) Following dialysis, an additional dose of 3.5-7mg/kg (0.035-0.07ml/kg) is recommended.

(5) Following dialysis, an additional dose of 5-10mg/kg (0.05-0.10 ml/kg) is recommended.

No dose adjustment is required in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, creatinine clearance may not adequately reflect renal impairment. Therefore, a 50% reduction in the daily maintenance dose is recommended when creatinine clearance is <60 ml/min/1.73m².

Pediatric population:

LEV-END® oral solution is used in babies and children under 4 years of age. In addition, the current dose strengths of LEV-END® tablets are not suitable for the initial treatment of children weighing less than 25 kg, for patients with swallowing difficulties and for dose administration below 250 mg. In all these cases, LEV-END® oral solution should be used.

The efficacy and safety of LEV-END® as monotherapy in children and adolescents under 16 years of age have not been established.

Geriatric population:

In elderly patients (65 years and older), dose adjustment if renal function is reduced is recommended (see section 4.2 Posology and method of administration, Renal/Liver 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 for use

Acute kidney injury

Acute kidney injury has been very rarely associated with levetiracetam use, with onset times ranging from a few days to several months.

Kidney failure

Dose adjustment may be required in patients with renal impairment. Therefore, it is recommended that renal function should be evaluated before dose selection in patients with severe hepatic impairment (*see section 4.2 Posology and method of administration*).

Blood cell counts

Rare cases of decreased blood cell counts (neutropenia, agranulocytosis, leukopenia, thrombocytopenia and pancytopenia) have generally been described in connection with levetiracetam administration at the beginning of treatment. A complete blood cell count is recommended in patients experiencing significant malaise, pyrexia, recurrent infections or coagulation disorders (*see section 4.8 Undesirable effects*).

Suicide

Suicide, suicide attempts, 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 showed a small increased risk of suicidal thoughts and behaviour. The mechanism of this risk is unknown.

Therefore, patients should be closely monitored for symptoms of depression, suicidal ideation and behavior and appropriate treatment should be considered. Patients and their relatives should be advised to seek medical support when symptoms of depression, suicidal ideation and behavior occur.

Unusual and aggressive behavior

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

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 levetiracetam or increasing the dose 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 postmarketing 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

Available data in children show no effect on puberty and growth. However, long-term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children are unknown.

Excipients

LEV-END® 100 mg/ml oral solution contains methyl parahydroxy benzoate (E218) and propyl parahydroxy benzoate (E216) and may cause allergic reactions (possibly delayed).

It also contains maltitol, patients with rare inherited fructose intolerance should not use this medicine.

LEV-END® oral solution, 100 mg/ml, contains less than 1 mmol (23 mg) of sodium in each dose and 70.5 mg of sodium in the maximal daily dose. This should be considered for patients on a controlled sodium diet.

LEV-END® oral solution contains less than 10 g glycerol per 1 ml dose. No glycerol-related adverse effects are expected due to the dose.

4. 5 Interaction with other medicinal products and other forms of interaction

Antiepileptic medicinal products

Data from pre-marketing clinical studies in adults show that levetiracetam does not affect the serum concentrations of existing antiepileptic drugs (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these drugs do not affect the pharmacokinetics of levetiracetam.

As in adults, there is no evidence of clinically relevant drug interactions in pediatric patients treated with doses up to 60 mg/kg/day.

In a retrospective evaluation of pharmacokinetic interactions in children and adolescents (4 to 17 years) with epilepsy, it was confirmed that levetiracetam taken orally as adjunctive therapy did not affect the steady-state concentration of carbamazepine and valproate administered concomitantly. However, data suggest that levetiracetam clearance is 20% higher in children receiving enzyme-inducing antiepileptic drugs. Dose adjustment is not necessary.

Probenecid

Probenecidine, a drug that blocks tubular secretion from the kidney (500 mg 4 times daily)

It has been shown to inhibit renal clearance of its primary metabolite but not levetiracetam. Despite this, the concentration of this metabolite remains low.

Methotrexate

Co-administration of methotrexate with levetiracetam has been reported to decrease methotrexate clearance, thereby increasing/extending the concentration of methotrexate in the blood to potentially toxic levels. Blood levels of methotrexate and levetiracetam should be carefully monitored in patients using these two drugs together.

Oral contraceptives and other pharmacokinetic interactions

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

Levetiracetam 2000 mg/day did not affect the pharmacokinetics of digoxin and warfarin; prothrombin times were unchanged. Concomitant use with digoxin, oral contraceptives and warfarin did not affect the pharmacokinetics of levetiracetam.

Laxatives

There are isolated reports of decreased levetiracetam efficacy with concomitant use of the osmotic laxative macrogol with oral levetiracetam. Therefore, oral macrogol should not be taken one hour before or one hour after levetiracetam.

Food and alcohol

Foods did not affect the amount of absorption of levetiracetam, but the rate of absorption was slightly reduced. There are no data on the interaction of levetiracetam with alcohol.

Additional information on special populations:

Pediatric population:

As in adults, in pediatric patients treated with doses up to 60 mg/kg/day, There is no evidence of a clinically relevant drug interaction.

A retrospective pharmacokinetic interaction evaluation in children and adolescents (4 to 17 years) with epilepsy confirmed that adjunctive treatment with oral levetiracetam did not affect the steady-state serum concentrations of co-administered carbamazepine and valproic acid. However, data showed that enzyme-inducing antiepileptics increased levetiracetam clearance by 20% in children. No dose adjustment is required.

4.6 Pregnancy and lactation

General Advice

Pregnancy category “C”.

Women of childbearing potential / Contraception

LEV-END® is not recommended in women of childbearing potential who do not use contraception unless clinically necessary.

Women of childbearing potential should seek specialist advice. Treatment with levetiracetam should be re-evaluated in women planning pregnancy. As with all antiepileptic drugs, abrupt discontinuation of treatment with levetiracetam should be avoided as this can lead to sudden seizures with serious consequences for the mother and her unborn child. Monotherapy should be preferred whenever possible because treatment with multiple antiepileptic drugs has been associated with a higher risk of congenital malformations than monotherapy due to concomitant antiepileptics.

Pregnancy

The large amount of post-marketing data from pregnant women exposed to levetiracetam monotherapy (more than 1800, of which more than 1500 exposures occurred in the first trimester of pregnancy) suggests no significant increased risk of major congenital malformations, although a teratogenic risk cannot be completely excluded. There is only limited evidence on the neural development of children exposed to levetiracetam monotherapy in utero. However, available epidemiologic studies (on approximately 100 children) do not indicate an increased risk of neurodevelopmental disorders or delays. Treatment with multiple antiepileptic drugs is associated with a higher risk of congenital malformations compared to monotherapy and monotherapy should therefore be considered. Minor developmental changes have been observed in animal studies (*see section 5.3 “Preclinical safety data”*).

Levetiracetam should not be used in pregnancy and women of childbearing potential unless clinically indicated. If, after careful consideration, it is considered clinically necessary, the lowest effective dose should be recommended.

Physiological changes during pregnancy may affect the concentration of levetiracetam. There have been reports of decreased levetiracetam concentrations during pregnancy. These decreases have been reported mostly in the third trimester (up to 60% basal concentration before pregnancy). It should be ensured that pregnant women treated with levetiracetam are clinically monitored.

Discontinuation of antiepileptic treatment may result in exacerbation of the disease, which may be harmful to the mother and fetus.

Lactation

Levetiracetam is excreted in breast milk. Therefore, breastfeeding is not recommended during treatment with LEV-END®. However, the benefits of breastfeeding for the child and the benefits of LEV-END® treatment for the breastfeeding mother should be taken into account when deciding whether to stop breastfeeding or to stop/avoid treatment with LEV-END®.

Fertility

Animal studies have shown that fertility is not affected (*see section 5.3 “Preclinical safety data”*). No clinical data are available, the potential risk to humans is unknown.

4.7 Effects on the use of vehicles and machinery

Levetiracetam has a minor or moderate effect on driving and using machines. Therefore, depending on possible different individual sensitivities, drowsiness or other central nervous system-related symptoms may occur, especially at the beginning of treatment or with dose increases. Caution is therefore recommended for persons performing tasks requiring dexterity, e.g. drivers of vehicles and machine operators. Patients performing such activities are not recommended to drive or operate machinery until it has been established that their skills are not affected.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions were nasopharyngitis, somnolence, headache, weakness and drowsiness. The adverse reaction profile given below is based on an analysis of pooled placebo-controlled clinical trials in which all indications were examined and a total of 3416

patients treated with levetiracetam. These data are supported by the use of levetiracetam in relevant open-label extension studies as well as post-marketing experience. The safety profile of levetiracetam is generally similar across age groups (adult and paediatric patients) and approved epilepsy indications.

Adverse reactions reported in clinical trials (adults, adolescents, children and infants >1 month) and postmarketing experience of the drug are listed below by system and frequency: Very common ($\geq 1/10$); common ($\geq 1/100$, $<1/10$); uncommon ($\geq 1/1000$, $<1/100$); rare ($\geq 1/10000$, $< 1/1000$); very rare ($< 1/10000$); unknown (cannot be estimated based on available data).

Infections and infestations

Very common: Nasopharyngitis

Rare: Infection

Blood and lymphatic system disorders

Uncommon: Thrombocytopenia, leucopenia

Rare: Neutropenia, pancytopenia, agranulocytosis

Immune system disorders

Rare: Drug reaction with eosinophilia and systemic symptoms (DRESS), hypersensitivity (including angioedema and anaphylaxis)

Metabolism and nutrition disorders

Common: Anorexy

Uncommon: Weight gain, weight decrease

Rare: Hyponatremia

Psychiatric disorders

Common: Depression, hostile behavior/aggression, anxiety, insomnia, irritability/irritability

Uncommon: Suicide attempt, suicidal ideation, psychotic disorders, conduct disorders, hallucinations, anger, confusional state, panic attack, emotional lability/mood swings, agitation

Rare: Suicide, personality disorders, abnormal thoughts, delirium

Very rare: Obsessive-compulsive disorder**

Nervous system disorders

Very Common: Somnolence, headache

Common: Convulsion, balance disorder, dizziness, lethargy, tremor

Uncommon: Amnesia, memory disorder, coordination disorder/ ataxia, paresthaesia, distractibility

Rare: choreoathetosis, dyskinesia, hyperkinesia, dysbasia, encephalopathy, seizure exacerbation, neuroleptic malignant syndrome *

Eye disorders

Uncommon: Double vision, blurred vision

Ear and inner ear disorders

Common: Vertigo

Cardiac disorders

Rare: Electrocardiogram QT prolongation

Respiratory, thoracic and mediastinal disorders

Common: Cough

Gastrointestinal disorders

Common: Abdominal pain, diarrhea, dyspepsy, nausea, vomiting

Rare: Pancreatitis

Hepatobiliary disorders

Uncommon: Abnormal liver function test values

Rare: Liver failure, hepatitis

Renal and urinary disorders

Rare: Acute kidney injury

Skin and subcutaneous tissue disorders

Common: Rash

Uncommon: Alopecia, eczema, itching

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

Musculoskeletal and connective tissue disorders

Uncommon: Muscle weakness, myalgia

Rare: Rhabdomyolysis and increased creatine phosphokinase in the blood*

General disorders and administration site conditions

Common: Astheny / weakness

Injury, poisoning and procedural complications

Uncommon: Injury

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

** At post-marketing follow-up, patients with a history of underlying obsessive-compulsive disorder (OCD) or psychiatric disorders very rarely developed obsessive-compulsive disorders.

Identification of selected adverse reactions

There is a higher risk of anorexia when topiramate is co-administered with levetiracetam. In several cases of alopecia, improvement was observed when levetiracetam treatment was discontinued.

Bone marrow suppression has been found in some cases of pancytopenia

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

Pediatric population

A total of 190 patients aged 1 month to 4 years were treated with levetiracetam in placebo-controlled and open-label extension studies. Of these patients, 60 were treated with levetiracetam in placebo-controlled studies. A total of 645 patients aged 4-16 years were treated with levetiracetam in placebo-controlled and open-label extension studies. Of these patients, 233 were treated with levetiracetam in placebo-controlled studies. The data obtained in both pediatric age groups are supported by post-marketing experience.

In addition, 101 infants under 12 months of age were included in a post-authorization safety study. No new safety concerns were identified in infants younger than 12 months with epilepsy.

The adverse reaction profile of levetiracetam is generally similar across age groups and approved epilepsy indications. Safety results in pediatric patients in placebo-controlled studies were consistent with the safety profile of levetiracetam, except for behavioral disorders and psychiatric conditions, which are 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%), conduct disorder (common, 5.6%) and lethargy (common, 3.9%) were the most commonly reported adverse effects compared to other age groups or the overall safety profile. In infants and children aged 1 month to 4 years, irritability (very common, 11.7%) and incoordination (common, 3.3%) were the most commonly reported adverse effects compared to other age groups or the overall safety profile..

A double-blind, placebo-controlled pediatric safety study with a non-inferiority design evaluated the cognitive and neurophysiological effects of levetiracetam in children aged 4-16 years with partial-onset seizures. For each protocol population, it was found that levetiracetam did not differ from placebo when considering the change from baseline in the Leiter-R Attention and Memory, Memory Screen Combined score. The results on behavioural and emotional functioning show a worsening on aggressive behaviour in levetiracetam-treated patients as measured by a standardized and systematic pathway using a validated instrument (CBCL-Achenbach Children's Behaviour Checklist). However, in the long-term open-label follow-up study, levetiracetam-treated subjects, on average, did not experience a worsening of their behavioral and emotional functioning, especially measures of aggressive behavior were not worse than baseline.

Reporting of side effects

Talk to your doctor, pharmacist or nurse if you experience any side effects listed or not listed in this leaflet. Also reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system

4.9 Overdose

Symptoms

Somnolence, agitation, aggression, confusion, respiratory depression and coma have been reported following levetiracetam overdose.

Treatment

After an acute overdose, the stomach can be emptied by gastric lavage or vomiting. Levetiracetam has no specific antidote. Overdose treatment should be symptomatic and may include

hemodialysis. Extraction efficiency by dialysis is 60% for levetiracetam and 74% for its primary metabolite.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, other antiepileptics

ATC code: N03AX14

Levetiracetam is a pyrrolidone derivative (S- enantiomer of α -ethyl-2-oxo-1-pyrrolidine acetamide) and has no chemical similarity to known antiepileptic drugs.

Mechanism of Action

The mechanism of action of levetiracetam is still not fully understood. In vitro and in vivo studies show that levetiracetam does not alter basic cell properties and normal neurotransmission.

In vitro studies have shown that levetiracetam affects intraneural Ca^{+2} levels by partially inhibiting N-type Ca^{+2} influx and reducing Ca^{+2} release from intraneural stores. In addition, it partially reverses the reduction in GABA and glycine-regulated currents induced by zinc and β -carbolines. In vitro studies have also shown that levetiracetam binds to a specific site in rodent brain tissue. This binding site is synaptic vesicle protein 2A, which is believed to be involved in vesicle fusion and neurotransmitter exocytosis. In a mouse model of audiogenic epilepsy, levetiracetam and related analogs show a correlation between their graded binding affinity to synaptic vesicle protein 2A and their ability to protect against seizures. These findings suggest that the interaction between levetiracetam and synaptic vesicle protein 2A contributes to the medicinal product's antiepileptic mechanism of action.

Pharmacodynamic Effects

Levetiracetam has been shown to increase protection against partial and primary generalized epileptic seizures in various animal models, without proconvulsant effects. Its primary metabolite is inactive. In humans, activity in both partial and generalized epilepsy conditions (epileptiform discharge/photoparoxysmal response) confirmed the broad-spectrum pharmacological profile of levetiracetam.

Clinical efficacy and safety

In patients over 1 month of age with infant, child and adult epilepsy for the adjunctive treatment of partial-onset seizures with or without secondary generalization:

In adults, the efficacy of levetiracetam administered in two equal doses, a total of 1000 mg, 2000 mg or 3000 mg daily, was demonstrated in 3 double-blind, placebo-controlled studies with a treatment duration of up to 18 weeks. In the pooled analysis, the percentage of patients who experienced a 50% or greater reduction in the weekly frequency of partial-onset seizures compared to baseline when a fixed dose was administered (12/14 weeks) was 27.7%, 31.6%, 41.3% and 12.6% in patients receiving 1000mg, 2000mg or 3000mg levetiracetam and placebo, respectively.

Pediatric population

The efficacy of levetiracetam in pediatric patients (4-16 years) was determined in a 14-week, double-blind, placebo-controlled study involving 198 patients. In this study, patients received levetiracetam at a fixed dose of 60 mg/kg/day (two doses per day).

In 44.6% of patients treated with levetiracetam and 19.6% of patients receiving placebo, the weekly frequency of partial-onset seizures decreased by 50% or more compared to baseline. In ongoing long-term treatment, 11.4% of patients achieved seizure-free status for at least 6 months and 7.2% for at least 1 year.

The effect of levetiracetam in pediatric patients (aged 1 month to less than 4 years) was determined in a double-blind placebo-controlled study involving 116 patients and a treatment duration of 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 charts. 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 the proportion of patients who responded (percentage of patients who showed a $\geq 50\%$ reduction from baseline in mean daily partial-onset seizure frequency), assessed by a blinded center reader using 48-hour video EEG. 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 were consistent across the age group. During ongoing long-term treatment, 8.6% of patients were seizure-free for at least 6 months and 7.8% for at least 1 year.

Thirty-five infants younger than 1 year with partial-onset seizures were enrolled in placebo-controlled clinical trials, only 13 of whom were younger than 6 months.

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

The efficacy of levetiracetam monotherapy was determined in a double-blind, parallel-group non-inferiority (equal-efficacy), double-blind, parallel-group non-inferiority study versus carbamazepine controlled release (CR) in 576 patients aged 16 years or older with a new or recent

diagnosis of epilepsy. Only patients with unprovoked partial-onset seizures or generalized tonic-clonic seizures were included in the study. Patients were randomized to either carbamazepine-CR 400-1200 mg/day or levetiracetam 1000-3000 mg/day and treatment was continued for up to 121 weeks depending on response.

Six-month seizure-free status was achieved in 73% of patients treated with levetiracetam and 72.8% of patients treated with carbamazepine-CR. The adjusted absolute difference between treatments was 0.2% (95% CI: -7.8 to 8.2%). More than half of the subjects remained seizure-free for 12 months (56.6% and 58.5% of subjects receiving levetiracetam and carbamazepine-CR, respectively). In a study reflecting clinical practice, concomitant antiepileptics were discontinued in a limited number of patients (36 of 69 adult patients) who responded to adjunctive treatment with levetiracetam.

Adjunctive treatment of myoclonic seizures in adolescents and adults over 12 years of age with juvenile myoclonic epilepsy

The efficacy of levetiracetam was confirmed in a 16-week, double-blind, placebo-controlled, double-blind study in patients aged 12 years and older with idiopathic generalized epilepsy with myoclonic seizures in different syndromes. The majority of patients had juvenile myoclonic epilepsy. The dose of levetiracetam administered in this study was a total of 3000 mg/day divided into two equal doses. A weekly reduction in myoclonic seizures of at least 50% was seen in 58.3% of patients treated with levetiracetam and 23.3% of patients receiving placebo.

In continued long-term treatment, 28.6% of patients spent at least 6 months and 21.0% at least 1 year without myoclonic seizures.

Adjunctive treatment of primary generalized tonic clonic seizures in adolescents and adults over 12 years of age with idiopathic generalized epilepsy

The efficacy of levetiracetam was confirmed in a 24-week, double-blind, placebo-controlled, double-blind, placebo-controlled study in adults, adolescents and a limited number of children with 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 waking). In this study, the levetiracetam dose was 3000 mg/day divided into two equal doses for adolescents and adults or 60 mg/kg/day divided into two equal doses for children.

A reduction of at least 50% in the weekly frequency of PGTC seizures was seen in 72.2% of patients treated with levetiracetam and 45.2% of patients receiving placebo. In continued long-term treatment, 47.4% of patients spent at least 6 months and 31.5% at least 1 year without tonic-clonic seizures.

5.2 Pharmacokinetic properties

General properties

The pharmacokinetic profile of levetiracetam, a substance with high solubility and permeability, is linear and has low individual or interindividual variability. There is no change in clearance with repeated administration. There is no valid evidence of gender, racial or circadian variability. Its pharmacokinetic profile is similar between healthy volunteers and patients with epilepsy.

Due to its complete and linear absorption, the plasma level of levetiracetam can be predicted based

on its oral dose expressed in mg/kg body weight. Therefore, plasma level monitoring is not required.

In adults and children, there is a significant correlation between salivary and plasma concentrations (4 hours after ingestion of the oral solution and for the oral tablet, the salivary/plasma concentration ratio is between 1 and 1.7).

Absorption:

Levetiracetam is rapidly absorbed after oral administration and its oral absolute bioavailability is close to 100%. Peak plasma concentration (C_{max}) is reached 1.3 hours after dose administration. Steady state is reached after two days of twice-daily administration.

The peak concentrations (C_{max}) following administration of a single 1000 mg dose and a total dose of 1000 mg administered twice daily are 31 and 43 microgram/ml, respectively. Absorption dose-independent and not affected by food.

Distribution:

There is no information on tissue distribution in humans. Binding of levetiracetam and its primary metabolite to plasma proteins is not significant (<10%). The volume of distribution is approximately 0.5 - 0.7 L/kg, which is close to the total body water volume.

Biotransformation:

Levetiracetam is not extensively metabolized in humans. The major metabolic pathway (24% of the dose) is enzymatic hydrolysis of the acetamide group. Hepatic cytochrome P450 isoforms are not involved in the formation of the primary metabolite ucb L057. Hydrolysis of the acetamide group is measurable in many tissues including blood cells. Ucb L057 metabolite is not pharmacologically active.

Two minor metabolites were also identified. One, 1.6% of the dose was obtained by hydroxylation of the pyrrolidone ring; the other, 0.9% of the dose was obtained by opening the pyrrolidone ring. Other unidentified compounds accounted for only 0.6% of the dose. No enantiomeric conversion between levetiracetam or its primary metabolite was detected in vivo.

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

Levetiracetam has little or no effect on CYP1A2, SULT1E1 or UGT1A1 activity in human liver cell cultures. Levetiracetam caused a slight induction of CYP2B6 and CYP3A4. In vitro data and in vivo interaction data with oral contraceptives, digoxin and warfarin indicate that no significant enzyme induction is expected in vivo. Therefore, no interaction of levetiracetam with other drugs or of other drugs with levetiracetam is expected.

Elimination:

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

Cumulative urinary excretion of levetiracetam and its primary metabolite accounts 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 followed by tubular reabsorption and its primary metabolite by active tubular secretion in addition to glomerular filtration. Levetiracetam elimination is related to creatinine clearance.

Characteristics in patients

Kidney/Liver failure:

The apparent body clearance of both levetiracetam and its primary metabolite is related to creatinine clearance. Therefore, in patients with moderate to severe renal impairment, it is recommended to adjust the daily dose of levetiracetam based on creatinine clearance. *(See section 4.2 Posology and method of administration)*

The half-life in adult patients with anuric end-stage renal failure is approximately 25 and 3.1 hours in the periods between and during dialysis, respectively. Fractional removal of levetiracetam in a typical 4-hour dialysis is 51%.

There is no change in the clearance of levetiracetam in patients with mild and moderate hepatic impairment. In patients with severe hepatic impairment, a decrease of more than 50% in levetiracetam clearance due to concomitant renal impairment has been shown. *(See section 4.2 Posology and method of administration)*

Pediatric population:

Children (4-12 years)

The plasma half-life of levetiracetam is 6 hours after a single oral dose of 20 mg/kg given to children with epilepsy aged 6-12 years. The apparent body weight-adjusted clearance of the drug is approximately 30% higher than in adults with epilepsy.

Following repeated oral dosing of 20 to 60 mg/kg/day in children with epilepsy aged 4-12 years, levetiracetam is rapidly absorbed. Peak plasma concentration is observed 0.5 to 1.0 hours after the dose. Dose-proportional and linear increases were observed for area under the curve and peak plasma concentrations. The elimination half-life is approximately 5 hours. Body clearance is 1.1 ml/min/kg.

Babies and children (1 month - 4 years)

Following administration of a single dose (20 mg/kg) of 100 mg/ml oral solution to epileptic infants and children aged 1 month to 4 years, levetiracetam was rapidly absorbed and peak plasma concentrations were observed approximately 1 hour after administration. Pharmacokinetic results showed that the half-life (5.3 hours) was shorter than in adults (7.2 hours) and drug clearance (1.5 ml/min/kg) was faster than in adults (0.96 ml/min/kg).

In a population pharmacokinetic analysis in patients aged 1 month to 16 years, body weight was significantly correlated with apparent clearance (increase in clearance with increase in body weight) and apparent volume of distribution. Age also has an effect on both parameters. This effect was seen in young babies, but attenuated with increasing age and became insignificant around 4 years of age.

In the pharmacokinetic analysis of both populations, levetiracetam coadministration with an enzyme-inducing antiepileptic drug resulted in an approximately 20% increase in levetiracetam clearance.

Gerontic population:

In the elderly, the half-life is increased by approximately 40% (10-11 hours) due to decreased renal function in this population (see section 4.2 Dosage and Administration).

5.3 Preclinical safety data

Preclinical data based on traditional safety pharmacology, genotoxicity and carcinogenicity potential studies have not revealed any specific hazard to humans.

Adverse effects not seen in clinical trials, but seen in rats and to a lesser extent in mouse, are adaptive response effects such as hepatic changes, weight gain, centrilobular hypertrophy, fatty infiltration, centrilobular hypertrophy, fatty infiltration and increased plasma liver enzymes, which are likely to be clinically relevant and occur at drug exposure levels similar to those in humans.

In studies in rats, at doses of 1800 mg/kg bw per day (6 times the maximum recommended dose for humans on a mg/m² basis), no adverse reactions to male or female fertility or reproductive performance in the mother/father and F1 offspring were observed.

Two embryo-fetal development (EFD) studies were conducted in rats at doses of 400, 1200 and 3600mg/kg/day. In only one of the 2 EFD studies at 3600mg/kg/day was there a slight decrease in fetal weight and associated increase in skeletal structure variability/minor anomalies. There was no effect on embryomortality and no increase in the incidence of malformations. The NOAEL (No Adverse Effect Level) is 3600mg/kg/day (12 times the maximum recommended dose in humans on a mg/m² basis) for pregnant female rats and 1200mg/kg/day for fetuses.

In rabbits, 4 embryo-fetal development studies were conducted covering doses of 200, 600, 800, 1200 and 1800mg/kg/day. At the 1800mg/kg/day dose level, it induced a significant maternal toxicity and a decrease in fetal weight.

Oral administration of levetiracetam to pregnant rabbits during the period of organogenesis resulted in increased embryofetal mortality and fetal skeletal abnormalities at doses of 600 mg/kg/day (4 times MRHD on a mg/m² basis), and decreased fetal weights and increased incidence of fetal malformations at doses of 1800 mg/kg/day (12 times MRHD on a mg/m² basis).

The dose with no developmental effects was 200 mg/kg/day (equivalent to MRHD in mg/m²). Maternal toxicity was also observed at 1800mg/kg/day.

This is associated with an increased incidence of fetuses with cardiovascular/skeletal abnormalities. The NOAEL is <200mg/kg/day for females and 200mg/kg/day for fetuses (equal to the maximum recommended dose in humans on a mg/m² basis).

Peri- and post-natal developmental studies were conducted in rats with levetiracetam doses of 70, 350 and 1800 mg/kg/day. The NOAEL was $\geq$ 1800 mg/kg/day (6 times the maximum recommended dose in humans on a mg/m² basis) for F0 females and for survival, growth and development of the F1 offspring until weaning.

In neonatal and juvenile animal studies in rats and dogs, no adverse effects were observed at doses up to 1800 mg/kg/day (corresponding to 6-17 times the maximum recommended dose in humans on a mg/m² basis) at any of the animals' standard developmental or maturation endpoints.

6. PHARMACEUTICAL CHARACTERISTICS

6.1 List of excipients

Sodium citrate dihydrate
Citric acid monohydrate
Methyl hydroxybenzoate (E218)
Propyl hydroxybenzoate (E216)
Ammonium glycyrrhizinate
Acesulfame potassium (E950)
Glycerol
Maltitol solution (E965)
Tutti frutti flavor
Deionized water

6.2 Incompatibilities

It has no determined incompatibilities, determined until today.

6.3 Shelf-life

24 months.

6.4 Special warnings for storage

Keep at room temperature below 25°C.
Keep in original packaging due to light sensitivity.

6.5 Nature and content of container

300 ml amber colored glass bottle with 1 plastic cap, graduated pipette, instructions for use, cardboard box.

6.6 The disposal of remnants of human medicinal product and other special precautions

Any unused medicinal product or waste material should be disposed of in accordance with the “Regulation on Medical Waste” and “Regulation on the Control of Packaging and Packaging Waste”.

7. MARKETING AUTHORIZATION HOLDER

Santa Farma İlaç San. A.Ş.

H. Edip Adıvar / Boru Çiçeği Sokak No 16, Şişli, İstanbul, Turkey

8. AUTHORIZATION NUMBER(S)

218/87

9. DATE OF FIRST APPROVAL/RENEWAL OF THE APPROVAL

Date of first authorization: 05.05.2009

Date of renewal of authorization: 05.05.2009

10. DATE OF REVISION OF THE TEXT

27.09.2018