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Package Insert

**LEVERA 250, 500 & 1000
(Levetiracetam Tablets
250 mg, 500 mg &
1000 mg)**

Name and strength of active ingredient

Levera 250
Levetiracetam Ph. Eur. 250 mg

Levera 500
Levetiracetam Ph. Eur. 500 mg

Levera 1000
Levetiracetam Ph. Eur. 1000 mg

Product Description

Levera 250
White to off white, oval, biconvex, film coated tablets debossed 'L 64' and breakline on one side and plain on other side.

Levera 500
Yellow coloured, oval, biconvex, film coated tablets debossed 'L 65' and breakline on one side and plain on other side.

Levera 1000
White to off white, oval, biconvex, film coated tablets debossed 'L 67' and breakline on one side and plain on other side.

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: antiepileptics, other antiepileptics, ATC code: N03AX14.

The active substance, Levetiracetam, is a pyrrolidone derivative (S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances.

Mechanism of action

The mechanism of action of Levetiracetam still remains to be fully elucidated. Levetiracetam does not alter basic cell characteristics and normal neurotransmission.

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

Pharmacodynamic effects

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

Pharmacokinetic properties

Levetiracetam is a highly soluble and permeable compound. The pharmacokinetic profile is linear with low intra- and inter-subject variability. There is no modification of the clearance after repeated administration. There is no evidence for any relevant gender, race or circadian variability. The pharmacokinetic profile is comparable in healthy volunteers and in patients with epilepsy. Due to its complete and linear absorption, plasma levels can be predicted from the oral dose of Levetiracetam expressed as mg/kg bodyweight. Therefore there is no need for plasma level monitoring of Levetiracetam.

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

Adults and adolescents

Absorption

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

Distribution

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

Biotransformation

Levetiracetam is not extensively metabolised in humans. The major metabolic pathway (24 % of the dose) is an enzymatic hydrolysis of the acetamide group. Production of the primary metabolite, ucb L057, is not supported by liver cytochrome P450 isoforms. Hydrolysis of the acetamide group was measurable in a large number of tissues including blood cells. The metabolite ucb L057 is pharmacologically inactive. Two minor metabolites were also identified. One was obtained by hydroxylation of the pyrrolidone ring (1.6 % of the dose) and the other one by opening of the pyrrolidone ring (0.9 % of the dose). Other unidentified components accounted only for 0.6 % of the dose. Enantiomeric interconversion does not occur for either Levetiracetam or its primary metabolite.

Levetiracetam and its primary metabolite have been shown not to inhibit the major human liver cytochrome P450 isoforms (CYP3A4, CYP2C9, CYP2C19, CYP2D6, 2E1 and 1A2), glucuronyl transferase (UGT1A1 and UGT1A8) and epoxide hydrolase activities. In addition, Levetiracetam does not affect the glucuronidation of valproic acid. In human hepatocytes in culture, Levetiracetam had little or no effect on CYP1A2, SUL1T1E1 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 substances, or vice versa, is unlikely.

Elimination

The plasma half-life in adults was 7±1 hours and did not vary either with dose, route of administration or repeated administration. The mean total body clearance was 0.96 ml/min/kg. The major route of excretion was via urine, accounting for a mean 95 % of the dose (approximately 93 % of the dose was excreted within 48 hours). Excretion via faeces accounted for only 0.3 % of the dose. The cumulative urinary excretion of Levetiracetam and its primary metabolite accounted for 66 % and 24 % of the dose, respectively during the first 48 hours. The renal clearance of Levetiracetam and ucb L057 is 0.6 and 4.2 ml/min/kg respectively indicating that Levetiracetam is excreted by glomerular filtration with subsequent tubular reabsorption and that the primary metabolite is also excreted by active tubular secretion in addition to glomerular filtration. Levetiracetam elimination is correlated to creatinine clearance.

Elderly

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

Renal impairment

The apparent body clearance of both Levetiracetam and of its primary metabolite is correlated to the creatinine clearance. It is therefore recommended to adjust the maintenance daily dose of Levetiracetam, based on creatinine clearance in patients with moderate and severe renal impairment. In anuric end-stage renal disease adult subjects the half-life was approximately 25 and 3.1 hours during interdialytic and intradialytic periods, respectively. The fractional removal of Levetiracetam was 51 % during a typical 4-hour dialysis session.

Hepatic impairment

In subjects with mild and moderate hepatic impairment, there was no relevant modification of the clearance of Levetiracetam. In most subjects with severe hepatic impairment, the clearance of Levetiracetam was reduced by more than 50 % due to a concomitant renal impairment.

Paediatric population

Children (4 to 12 years)

Following single oral dose administration (20 mg/kg) to epileptic children (6 to 12 years), the half-life of Levetiracetam was 6.0 hours. The apparent body weight adjusted clearance was approximately 30 % higher than in epileptic adults. Following repeated oral dose administration (20 to 60 mg/kg/day) to epileptic children (4 to 12 years), Levetiracetam was rapidly absorbed. Peak plasma concentration was observed 0.5 to 1.0 hour after dosing. Linear and dose proportional increases were observed for peak plasma concentrations and area under the curve. The elimination half-life was approximately 5 hours. The apparent body clearance was 11.1 ml/min/kg.

Infants and children (1 month to 4 years)

Following single dose administration (20 mg/kg) of a 100 mg/ml oral solution to epileptic children (1 month to 4 years), Levetiracetam was rapidly absorbed and peak plasma concentrations were observed approximately 1 hour after dosing. The pharmacokinetic results indicated that half-life was shorter (5.3 h) than for adults (7.2 h) and apparent clearance was faster (1.5 ml/min/kg) than for adults (0.96

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

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

Indication/Usage

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

Levetiracetam is indicated as adjunctive therapy

- in the treatment of partial onset seizures with or without secondary generalisation in adults and children from 4 years of age with epilepsy;
- in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy;
- in the treatment of primary generalised tonic-clonic seizures in adults and children from 12 years of age with Idiopathic Generalised Epilepsy.

Posology and method of administration

Dosage and Administration
Levetiracetam therapy can be initiated with either intravenous or oral administration. Conversion to or from oral to intravenous administration can be done directly without titration. The total daily dose and frequency of administration should be maintained.

The tablets must be taken orally, swallowed with a sufficient quantity of liquid and may be taken with or without food. After oral administration the bitter taste of Levetiracetam may be experienced. The daily dose is administered in two equally divided doses.

Route of Administration

For oral use.

Adults

Monotherapy

Adults and adolescents from 16 years of age
The recommended starting dose is 250 mg twice daily which should be increased to an initial therapeutic dose of 500 mg twice daily after two weeks. The dose can be further increased by 250 mg twice daily every two weeks depending upon the clinical response. The maximum dose is 1500 mg twice daily.

Add-on therapy

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

The initial therapeutic dose is 500 mg twice daily. This dose can be started on the first day of treatment.

Depending upon the clinical response and tolerability, the daily dose can be increased up to 1500 mg twice daily. Dose changes can be made in 500 mg twice daily increases or decreases every two to four weeks.

Children

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

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

Monotherapy

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

Add-on therapy

Add-on therapy for children (4 to 11 years) and adolescents (12 to 17 years) weighing less than 50 kg

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

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

The initial therapeutic dose is 10 mg/kg twice daily.

Depending upon the clinical response and tolerability, the dose can be increased up to 30 mg/kg twice daily. Dose changes should not exceed increases or decreases of 10 mg/kg twice daily every two weeks.

The lowest effective dose should be used.

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

Dose recommendations for children and adolescents:

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

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

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

Elderly

Adjustment of the dose is recommended in elderly patients with compromised renal function.

Renal impairment

The daily dose must be individualised according to renal function (see Section Warnings and Precautions).

For adult patients, refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CL_{cr}) in ml/min is needed. The CL_{cr} in ml/min may be estimated from serum creatinine (mg/dl) determination, for adults and adolescents weighing 50 kg or more, using the following formula:

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

Then CL_{cr} is adjusted for body surface area (BSA) as follows:

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

Dosing adjustment for adult and adolescent patients weighing more than 50kg with impaired renal function.

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

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

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

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

The CL_{cr} in ml/min/1.73 m² may be estimated from serum creatinine (mg/dl) determination using, for young adolescents and children using the following formula (Schwartz formula):

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

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

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

Group	Creatinine clearance (ml/min/1.73m ²)	Children and adolescents weighing less than 50 kg
Normal	> 80	10 to 30 mg/kg (0.10 to 0.30 ml/kg) twice daily
Mild	50-79	10 to 20 mg/kg (0.10 to 0.20 ml/kg) twice daily

Moderate	30-49	5 to 15 mg/kg (0.05 to 0.15 ml/kg) twice daily
Severe	< 30	5 to 10 mg/kg (0.05 to 0.10 ml/kg) twice daily
End-stage renal disease patients undergoing dialysis	-	10 to 20 mg/kg (0.10 to 0.20 ml/kg) once daily ⁽²⁾

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

⁽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 to 10 mg/kg (0.05 to 0.10 ml/kg) supplemental dose is recommended.

Hepatic impairment

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

Route of Administration

Oral use

Contraindication

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

Special warnings and precautions for use

Renal impairment

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

Acute Kidney injury

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

Blood cell counts

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

Suicide

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

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

Paediatric population

The tablet formulation is not adapted for use in infants and children under the age of 6 years. Available data in children did not suggest impact on growth and puberty. However, long term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children remain unknown.

Pregnancy and Lactation

Women of child bearing potential

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

Pregnancy

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

Levetiracetam can be used during pregnancy, if after careful assessment it is considered clinically needed. In such case, the lowest effective dose is recommended.

Physiological changes during pregnancy may affect Levetiracetam concentration. Decrease in Levetiracetam plasma concentrations has been observed during pregnancy. This decrease is more pronounced during the third trimester (up to 60% of baseline concentration before pregnancy). Appropriate clinical management of pregnant women treated with Levetiracetam should be ensured.

Breastfeeding

Levetiracetam is excreted in human breast milk. Therefore, breast-feeding is not recommended.

However, if Levetiracetam treatment is needed during breastfeeding, the benefit/risk of the treatment should be weighed considering the importance of breastfeeding.

Fertility

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

Interactions with Other Medicaments

Antiepileptic medicinal products

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

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

A retrospective assessment of pharmacokinetic interactions in children and adolescents with epilepsy (4 to 17 years) confirmed that adjunctive therapy with orally administered Levetiracetam did not influence the steady-state serum concentrations of concomitantly administered carbamazepine and valproate. However, data suggested a 20 % higher Levetiracetam clearance in children taking enzyme-inducing antiepileptic medicinal products. Dose adjustment is not required.

Probenecid

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

Methotrexate

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

Oral contraceptives and other pharmacokinetics interactions

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

Laxatives

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

Food