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INSTRUCTION
for medical use

LOGUFEN®

Composition:
active substance: levetiracetam;
1 film-coated tablet contains levetiracetam 250 mg or 500 mg;
excipients: maize starch, povidone, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate;
coating content:
250 mg tablets: Opadry (II) 85G68918 white (polyvinyl alcohol, titanium dioxide (E 171), talc, polyethylene glycol, lecithin);
500 mg tablets: Opadry (II) 85G52482 yellow (alcohol polyvinyl, talc, titanium dioxide (E 171), polyethylene glycol, lecithin, iron oxide yellow (E 172)).

Pharmaceutical form. Film-coated tablets.
Main physical and chemical properties:
250 mg tablets: white to off white color, oval shape, film-coated tablets, with break line on one side;
500 mg tablets: yellow color, oval shape, film-coated tablets, with break line on one side.

Pharmacotherapeutic group. Antiepileptics. Levetiracetam.
ATC code: N03A X14.

Pharmacological properties.
Pharmacodynamics.
Levetiracetam is a derivative of pyrrolidone (S-enantiomer alpha-ethyl-2-oxo-1-pyrrolidine-acetamide), differing in its chemical structure from known antiepileptic drugs.
Mechanism of action
The mechanism of action of levetiracetam still remains to be fully elucidated. *In vitro* and *in vivo* experiments suggest that levetiracetam does not alter basic nerve cell characteristics and normal neurotransmission. *In vitro* studies show that levetiracetam affects intraneuronal Ca^{2+} levels by partial inhibition of N-type Ca^{2+} currents and by reducing the release of Ca^{2+} from intraneuronal stores. In addition, it partially reverses the reductions in GABA- and glycine-gated currents induced by zinc and β-carbolines. Furthermore, levetiracetam has been shown in *in vitro* studies to bind to a specific site in rodent brain tissue. This binding site is the synaptic vesicle protein 2A, believed to be involved in vesicle fusion and neurotransmitter exocytosis. Levetiracetam and related analogues show a rank order of affinity for binding to the synaptic vesicle protein 2A which correlates with the potency of their anti-seizure protection in the mouse audiogenic model of

epilepsy. This finding suggests that the interaction between levetiracetam and the synaptic vesicle protein 2A seems to contribute to the antiepileptic mechanism of action of the drug.

Pharmacodynamic effects

Levetiracetam induces 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 man, an activity in both partial and generalized 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, time independent, with low intra- and inter-subject variability. There is no modification of the clearance after repeated administration. There is no evidence for any relevant gender, race, or circadian variability. The pharmacokinetic profile is comparable in healthy volunteers and in patients with epilepsy.

Due to its complete and linear absorption, plasma levels can be predicted from the oral dose of levetiracetam expressed as milligram (mg) per kilogram (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 the oral tablets and after 4 hours post-dose for an oral solution formulation).

Adults and adolescents

Absorption

Levetiracetam is rapidly absorbed after oral administration. Oral absolute bioavailability is close to 100%. Peak plasma concentration (C_{max}) is achieved at 1.3 hours after dosing. Steady state is achieved after two days of a twice daily administration schedule. C_{max} are typically 31 µg/ml and 43 µg/ml following a single 1000 mg dose and repeated 1000 mg b.i.d. dose respectively. The extent of absorption is dose-independent and is not altered by food.

Distribution

No tissue distribution data are available in humans. Neither levetiracetam nor its major 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 volume of distribution of intracellular and extracellular water.

Metabolism

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

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

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

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

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

In human hepatocytes in culture, levetiracetam had little or no effect on conjugation of CYP1A2, SULT1E1 or UGT1A1. High concentrations of levetiracetam (680 µg/ml) caused mild induction of CYP2B6 and CYP3A4; however, in concentrations similar to C_{max} after repeated administration

of 1500 mg twice daily, this effect was not biologically significant. 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 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 feces 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 ml/min/kg and 4.2 ml/min/kg respectively indicating that levetiracetam is excreted by glomerular filtration with subsequent tubular reabsorption and that the primary metabolite is also excreted by active tubular secretion in addition to glomerular filtration. Levetiracetam elimination is correlated to creatinine clearance.

Elderly

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

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 (see "Posology and method of administration" section).

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

Hepatic impairment

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

Pediatric population

Children (4 to 12 years of age)

Following single dose administration (20 mg/kg) to epileptic children (6 to 12 years of age), the half-life of levetiracetam was 6 hours. The apparent body clearance corrected based on body weight 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 of age), levetiracetam was rapidly absorbed. C_{max} was observed 0.5 to 1.0 hour after dosing. Linear and dose proportional increases were observed for C_{max} and area under the pharmacokinetic drug concentration-time curve (AUC). The elimination half-life was approximately 5 hours. The apparent body clearance was 1.1 ml/min/kg.

Clinical particulars.

Indications.

Monotherapy (drug of first choice) in the treatment of:

- partial onset seizures with or without secondary generalization in patients from 16 years of age with newly diagnosed epilepsy.

Adjunctive therapy in the treatment of:

- partial onset seizures with or without secondary generalization in adults and children from 6 years of age with epilepsy;
- myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy;
- primary generalized convulsive (tonic-clonic) seizures in adults and adolescents from 12 years of age with idiopathic generalized epilepsy.

Contraindications.
Hypersensitivity to levetiracetam or other pyrrolidone derivatives or any of the drug excipients.

Interaction with other medicinal products and other forms of interaction.
Antiepileptics.
Data from clinical studies conducted in adults indicate that levetiracetam does not influence serum concentrations of existing antiepileptic drugs (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin, and primidone); and these antiepileptic medicinal products do not influence the pharmacokinetics of levetiracetam.
As in adults, there is no evidence of clinically significant medicinal product interactions in pediatric 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
It has been reported that the simultaneous administration of levetiracetam and methotrexate reduces the clearance of methotrexate, which leads to an increase/prolongation of the concentration of methotrexate in the blood to potentially toxic levels. The levels of methotrexate and levetiracetam in the blood should be carefully monitored in patients receiving treatment with two drugs at the same time.
Oral contraceptives and other pharmacokinetics interactions
Levetiracetam 1000 mg daily did not influence the pharmacokinetics of oral contraceptives (ethinylestradiol and levonorgestrel); endocrine parameters (luteinizing hormone and progesterone) were not modified. Levetiracetam 2000 mg daily did not influence the pharmacokinetics of digoxin and warfarin; prothrombin times values were not modified. Co-administration with digoxin, oral contraceptives and warfarin did not influence the pharmacokinetics of levetiracetam.
Laxatives
In some cases, reduction of the efficacy of levetiracetam with the simultaneous application of the macrogolomic osmotic laxative with oral levetiracetam was reported. Therefore, you should not take macrogol orally within one hour before and within one hour after taking levetiracetam.
Food and alcohol
The extent of absorption of levetiracetam was not altered by food intake, but the rate of absorption was slightly reduced when taken with food. No data on the interaction of levetiracetam with alcohol are available.

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 "Posology and method of administration" section).

Acute kidney injury

The use of levetiracetam has been very 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 (see "Adverse reactions" section).

Suicide

Suicide, suicide attempt, suicidal ideation and behavior have been reported in patients treated with antiepileptic agents (including levetiracetam). A meta-analysis of randomized placebo-controlled trials of antiepileptic medicinal products has shown a small increased risk of suicidal thoughts and behavior. The mechanism of this risk is not known. Therefore, patients should be monitored 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.

Abnormal and aggressive behaviors

Levetiracetam may cause psychotic symptoms and behavioral abnormalities including irritability and aggressiveness. Patients treated with levetiracetam should be monitored for developing psychiatric signs suggesting important mood and/or personality changes. If such behaviors are noticed, treatment adaptation or gradual discontinuation should be considered. If discontinuation is considered, please refer to "Posology and method of administration" section.

Worsening of seizures

As with other types of antiepileptic drugs, levetiracetam may rarely exacerbate seizure frequency or severity. This paradoxical effect was mostly reported within the first month after levetiracetam initiation or increase of the dose, and was reversible upon drug discontinuation or dose decrease.

Patients should be advised to consult their physician immediately in case of aggravation of epilepsy. Lack of efficacy or seizure worsening has for example been reported in patients with epilepsy associated with sodium voltage-gated channel alpha subunit 8 (SCN8A) mutations.

Electrocardiogram (ECG) QT interval prolongation

Rare cases of ECG QT interval prolongation have been observed during the post-marketing surveillance. Levetiracetam should be used with caution in patients with QTc-interval prolongation, in patients concomitantly treated with drugs affecting the QTc-interval, or in patients with relevant preexisting cardiac disease or electrolyte disturbances.

Pediatric 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 reproductive age

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 post-marketing data on pregnant women exposed to levetiracetam monotherapy (more than 1800, among which in more than 1500 exposure occurred during the first 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 levetiracetam monotherapy *in utero*. However, current epidemiological studies (on about 100 children) 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, breastfeeding is not recommended. However, if levetiracetam treatment is needed during breastfeeding, the benefit/risk of the treatment should be weighed considering the importance of breastfeeding.

Fertility

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

Effects on ability to drive and use machines.

Levetiracetam has minor or moderate influence on the ability to drive and use machines. Due to possible different individual sensitivity, some patients might experience somnolence or other central nervous system related symptoms, especially at the beginning of treatment or following a dose increase. Therefore, caution is recommended in those patients when performing tasks that require increased concentration, 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.

Posology and method of administration.

Tablets should be taken orally, swallowed with a sufficient quantity of liquid, 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.

Partial onset seizures

The recommended dosing for monotherapy (from 16 years of age) and adjunctive therapy is the same; as outlined below.

All indications

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

The initial therapeutic dose is 500 mg twice daily. This dose can be started on the first day of treatment. However, a lower initial dose of 250 mg twice daily may be given based on physician

assessment of seizure reduction versus potential side effects. This can be increased to 500 mg twice daily after two weeks.
Depending upon the clinical response and tolerability, the daily dose can be increased up to maximal 1,500 mg twice daily. Dose changes can be made in 250 mg or 500 mg twice daily every two to four weeks.
Children from 6 years of age and adolescents (12 to 17 years) weighing below 50 kg
The physician should prescribe the most appropriate presentation, strength, and pharmaceutical form, according to weight, age and dose. Refer to "Pediatric population" section for dosing adjustments based on weight.
Discontinuation
If levetiracetam has to be discontinued it is recommended to withdraw it gradually (e.g. in adults and adolescents weighing more than 50 kg: 500 mg decreases twice daily every two to four weeks; in children and adolescents weighing less than 50 kg: dose decrease should not exceed 10 mg/kg twice daily every two weeks).
Special populations
Elderly (65 years and older)
Adjustment of the dose is recommended in elderly patients with compromised renal function (see "Renal impairment" section).
Renal impairment
The daily dose must be individualized according to renal function.
For adult patients, refer to the following table and adjust the dose as indicated.
To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in ml/min is needed.
The CLcr may be estimated from serum creatinine determination, for adults and adolescents weighing 50 kg or more, using the following formula:

$$\text{CLcr (ml/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} \times 0{,}85 \text{ (for women).}$$

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

$$\text{CLcr (ml/min/1.73 m}^2\text{)} = \frac{\text{CLcr (ml/min)}}{\text{BSA subject (m}^2\text{)}} \times 1{,}73.$$

Table 1
Dosing adjustment for adult and adolescent patients weighing more than 50 kg with impaired renal function

Degree of severity of renal insufficiency	Creatinine clearance (ml/min/1.73 m^2)	Dose and frequency
Normal renal function	≥80	500 to 1500 mg twice daily
Mild	50–79	500 to 1000 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 1000 mg once daily[(2)]

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

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

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 m^2 may be estimated from serum creatinine (mg/dl) determination, for adolescents, children, and infants, using the following formula (Schwartz formula):

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

In children to less than 13 years and adolescent female ks = 0,55; in adolescent male ks = 0.7.

Table 2
Dosing adjustment for children (aged 6 and above) and adolescents patients weighing less than 50 kg with impaired renal function

Degree of severity of renal insufficiency	Creatinine clearance (ml/min/1.73 m^2)	Children (aged 6 and above) and adolescents patients weighing less than 50 kg
Normal renal function	≥80	10 to 30 mg/kg (0,10–0,30 ml/kg) twice daily
Mild	50–79	10 to 20 mg/kg (0,10–0,20 ml/kg) twice daily
Moderate	30–49	5 to 15 mg/kg (0,05–0,15 ml/kg) twice daily
Severe	<30	5 to 10 mg/kg (0,05–0,10 ml/kg) twice daily
End-stage renal disease (patients undergoing dialysis)	-	10 to 20 mg/kg (0,10–0,20 ml/kg) once daily(2)(3)

(1) Oral levetiracetam solution (100 mg/ml) 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 levetiracetam dose is recommended on the first day of treatment.
(3) Following dialysis, a 5 to 10 mg/kg (0.05–0.10 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 severity. Therefore a 50% reduction of the daily maintenance dose is recommended when the creatinine clearance is <60 ml/min/1.73 m^2.
Pediatric population
The physician should prescribe the most appropriate presentation, strength, and pharmaceutical form according to age, weight, and dose.
The tablet formulation is not adapted for use in children under the age of 6 years. Oral levetiracetam 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. Age limits due to the form of the disease are given in the “Indications” section. In all of the above cases oral levetiracetam 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.
No data are available.
Adolescents (16 and 17 years of age) weighing 50 kg or more with partial onset seizures with or without secondary generalization with newly diagnosed epilepsy
Please refer to the above section on *"Adults (≥18 years) and adolescents (12 to 17 years) weighing 50 kg or more"*.
Add-on therapy for children from 6 years of age and adolescents (12 to 17 years) weighing below 50 kg
An oral solution is the preferred formulation for use in infants and children under the age of 6 years.
For children 6 years and above, an 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 lowest effective dose should be used for all indications. The starting dose for a child or adolescent of 25 kg should be 250 mg twice daily with a maximum dose of 750 mg twice daily.
Dose in children 50 kg or greater is the same as in adults for all indications.
Please refer to the above section on "Adults (≥18 years) and adolescents (12 to 17 years) weighing 50 kg" or more for all indications.
Add-on therapy for infants aged from 1 month to less than 6 months
An oral solution is the formulation to use in infants.

Pediatric population.
Levetiracetam in tablet formulation is not adapted for use in children under the age of 6 years. Infants from 1 month and children under 6 years of age should use oral levetiracetam solution.

Overdose.
Symptoms
Somnolence, agitation, aggression, respiratory depression, depressed level of consciousness and coma were observed with levetiracetam overdoses.
Management of overdose
After an acute overdose, the stomach may be emptied by gastric lavage or by induction of emesis. There is no specific antidote for levetiracetam. If necessary, symptomatic treatment is conducted, and may include hemodialysis (extraction efficiency is 60% for levetiracetam and 74% for the primary metabolite).

Adverse reactions.
The most frequently reported adverse reactions were nasopharyngitis, somnolence, headache, fatigue, and dizziness. The adverse reaction profile presented below is based on the analysis of pooled placebo-controlled clinical trials. These data are supplemented with the use of levetiracetam in corresponding open-label extension studies, as well as post-marketing experience. The safety profile of levetiracetam is generally similar across age groups (adult and pediatric patients) and across the approved epilepsy indications.
Adverse reactions reported in clinical studies (adults, adolescents, children and infants >1 month) and from post-marketing experience are listed in the following table per System Organ Class and per frequency. Adverse reactions are presented in the order of decreasing seriousness and their frequency is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1,000) and very rare (<1/10000).

Table 3

MedDRA System Organ Class	Frequency category				
	Very common	Common	Uncommon	Rare	Very rare
Infections and infestations	Nasopharyngitis			Infection	
Blood and lymphatic system disorders			Thrombocytopenia, leukopenia	Pancytopenia, neutropenia, agranulocytosis	
Immune system disorders				Drug reaction with eosinophilia and systemic symptoms (DRESS), hypersensitivity (including angioedema and anaphylaxis)	
Metabolism and nutrition disorders		Anorexia	Weight decreased, weight increase	Hyponatremia	
Psychiatric disorders		Depression, hostility/aggression, anxiety, insomnia, nervousness /irritability	Suicide attempt, suicidal ideation, psychotic disorder, abnormal behavior, hallucination, anger, confusional state, panic attack, affect lability / mood swings, agitation	Suicide, personality disorder, thinking abnormal, delirium	Obsessive-compulsive disorder**
Nervous system disorders	Somnolence, headache	Convulsion, balance disorder, dizziness, lethargy, tremor	Amnesia, memory impairment, coordination abnormal/ataxia, paresthesia, disturbance in attention	Choreoathetosis, dyskinesia, hyperkinesia, gait disturbance, encephalopathy, seizures aggravated, neuroleptic malignant syndrome*	
Eye disorders			Diplopia, vision blurred		
Ear and labyrinth disorders		Vertigo			

Cardiac disorders				Electrocardiogram QT prolonged	
Respiratory, thoracic and mediastinal disorders		Cough			
Gastrointestinal disorders		Abdominal pain, diarrhea, dyspepsia, vomiting, nausea		Pancreatitis	
Hepatobiliary disorders			Liver function test abnormal	Hepatic failure, hepatitis	
Renal and urinary disorders				Acute kidney injury	
Skin and subcutaneous tissue disorders		Rash	Alopecia, eczema, pruritus	Toxic epidermal necrolysis, Stevens–Johnson syndrome, erythema multiforme	
Musculoskeletal and connective tissue disorders			Muscular weakness, myalgia	Rhabdomyolysis and blood creatine phosphokinase increased*	
General disorders		Asthenia/ fatigue			
Injury, poisoning and procedural complications			Injury		

* Prevalence is significantly higher in Japanese patients when compared to non-Japanese patients.
** Very rare cases of development of obsessive-compulsive disorders (OCD) in patients with underlying history of OCD or psychiatric disorders have been observed in post-marketing surveillance.

Description of selected adverse reactions.
The risk of anorexia is higher when levetiracetam is co-administered with topiramate. In several cases of alopecia, recovery was observed when levetiracetam was discontinued.
Bone marrow suppression was identified in some of the cases of pancytopenia. Cases of encephalopathy generally occurred at the beginning of the treatment (few days to a few months) and were reversible after treatment discontinuation.
Pediatric population
The adverse reaction profile of levetiracetam is generally similar across age groups and across the approved epilepsy indications. Safety results in pediatric patients in placebo-controlled clinical studies were consistent with the safety profile of levetiracetam in adults except for behavioral 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%), affect lability (common, 1.7%), aggression (common, 8.2%), abnormal behavior (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 abnormal (common, 3.3%) were reported more frequently than in other age groups or in the overall safety profile.
Assessment of levetiracetam effects the cognitive and neuropsychological in children 4 to 16 years of age with partial onset seizures showed that levetiracetam was not different (non-inferior) from placebo with regard to the change from baseline of the Leiter-R Attention and Memory, Memory Screen Composite score in the per-protocol population. Results related to behavioral and emotional functioning indicated a worsening in levetiracetam treated patients on aggressive behavior as measured in a standardized and systematic way using a validated instrument (CBCL – Achenbach Child Behavior Checklist). However, subjects, who took levetiracetam in the long-term open label follow-up study, did not experience a worsening, on average, in their behavioral and emotional functioning; in particular measures of aggressive behavior were not worse than baseline.
Reporting of suspected adverse reactions.
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. Medical and pharmaceutical workers, as well as patients or their legal representatives are asked to report any suspected adverse reactions and lack of effectiveness of the medicinal product through the Pharmacovigilance Automated Information System at: https://aisf.dec.gov.ua.

Shelf life.
2 years.

Storage conditions.
Store in original package at temperature below 25°C.
Keep out of reach of children.

Package.
10 tablets in a blister; 3 or 6 blisters in a carton pack.

Conditions of supply.
By prescription.

Manufacturer.
KUSUM HEALTHCARE PVT LTD.

Location of manufacturer and its address of business activity.
SP-289 (A), RIICO Industrial area, Chopanki, Bhiwadi, Dist. Alwar (Rajasthan), India.

Date of last revision.