APPROVED
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INSTRUCTION
for medical use

LOGUFEN®

Composition:
active substance: levetiracetam;
1 ml of solution contains levetiracetam 100 mg;
excipients: liquid maltitol (E 965), methyl parahydroxybenzoate (E 218), propyl parahydroxybenzote (E 216), glycerol, acesulfame potassium (E 950), citric acid anhydrous, sodium citrate, sodium dihydrogen phosphate, dihydrate, sodium hydroxide, flavor "Lemon", purified water.

Pharmaceutical form. Oral solution.
Basic physico-chemical properties: clear solution with a characteristic odor.

Pharmacotherapeutic group. Anti-epileptics. Levetiracetam.
ATC code N03A X14.

Pharmacological properties.
Pharmacodynamics.
Levetiracetam is a pyrrolidone derivative (S-enantiomer of alpha-ethyl-2-oxo-1-pyrrolidine-acetamide), its chemical structure differs from known anti-epileptics.
The mechanism of action of levetiracetam has not been sufficiently studied, but it has been determined that it differs from the mechanism of action of known anti-epileptic drugs. *In vitro* and *in vivo* studies 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+} channel 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 specific sites in rodent brain tissues. This binding site is the synaptic vesicle protein 2A involved in vesicle fusion and neurotransmitter release. Levetiracetam and related analogs show a rank order of affinity for binding to the synaptic vesicle protein 2A which correlates with the potency of their anti-seizure protection in the mouse audiogenic model of epilepsy. These findings suggest that the interaction between levetiracetam and the synaptic vesicle protein 2A may partially explain the anti-epileptic mechanism of action of the medicinal product.
Levetiracetam provides 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 humans, the activity of the drug is confirmed for both partial and generalized seizures (epileptiform discharge/photoparoxysmal response) which indicates a broad spectrum of the pharmacological profile of levetiracetam.
Pharmacokinetics.
Levetiracetam is highly soluble and permeable. The pharmacokinetics is linear, does not depend on time and is characterized by low inter- and intra-subject variability. The clearance is not

modified after repeated administration of the drug. There is no evidence of any influence of gender, race or circadian rhythm on the pharmacokinetics. The pharmacokinetic profile is comparable in healthy volunteers and in patients with epilepsy.
Due to complete and linear absorption plasma levels of the drug can be predicted based on the oral dose of levetiracetam expressed in mg/kg of 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 (the ratio of saliva/plasma concentrations ranged from 1 to 1,7 after oral tablet administration and 4 hours after administration of oral solution).
Adults and adolescents
Absorption
Levetiracetam is rapidly absorbed after oral administration. Absolute oral bioavailability is close to 100 %. Peak plasma concentration (Cmax) is achieved 1.3 hours after administration of the drug. Steady state is achieved after 2 days of administering the drug twice daily. Cmax is typically 31 µg/ml and 43 µg/ml following a single 1000 mg dose and a repeated 1000 mg twice daily dose, respectively. The extent of absorption is dose-independent and is not altered by food.
Distribution
No data about drug distribution in human tissues are available. Neither levetiracetam, nor its primary metabolite are significantly bound to plasma proteins (<10 %). The volume of distribution of levetiracetam ranges from 0.5 to 0.7 l/kg, which is close to the total body water volume.
Metabolism
Levetiracetam is not extensively metabolized in humans. The major metabolic pathway (24 % of the dose) is 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 observed 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.
During *in vitro* studies, levetiracetam and its primary metabolite did not inhibit the activity of the major human liver cytochrome P450 isoforms (CYP3A4, 2A6, 2C9, 2C19, 2D6, 2E1 and 1A2), glucuronyltransferase (UGT1A1 and UGT1A6) and epoxide hydroxylase. In addition, levetiracetam does not inhibit the *in vitro* glucuronidation of valproic acid.
In human hepatocytes in culture, levetiracetam had little or no effect on the conjugation of CYP1A1/2, SULT1E1 and 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 medicinal products or vice versa is unlikely.
Elimination
The plasma half-life in adults was 7±1 hours and did not depend on the dose, route of administration or repeated administration. The mean total body clearance was 0.96 ml/min/kg.
The majority of the drug, a mean of 95 % of the dose, was excreted by kidneys (approximately 93 % of the dose was excreted within 48 hours). Only 0.3 % of the dose was excreted with feces.
The cumulative urinary excretion of levetiracetam and its primary metabolite accounted for 66 % and 24 % of the dose, respectively, during the first 48 hours. The renal clearance of levetiracetam and ucb L057 is 0.6 and 4.2 ml/min/kg, respectively, 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 approximately 40 % (10-11 hours). This is related to the decreased in renal function in this population (see section "Dosage and administration").
Renal impairment
The apparent total body clearance of levetiracetam and its primary metabolite is correlated with creatinine clearance. It is therefore recommended to adjust the maintenance daily dose of levetiracetam in patients with moderate and severe renal impairment based on creatinine clearance (see section "Dosage and administration").
In anuric end-stage renal disease patients the half-life was approximately 25 and 3.1 hours during interdialytic and intradialytic periods, respectively. 51 % of levetiracetam was removed during a typical 4-hour dialysis session.
Hepatic impairment
In patients with mild and moderate hepatic impairment, no relevant changes of the clearance of levetiracetam were observed. In most patients with severe hepatic impairment, the clearance of levetiracetam was reduced by more than 50 % due to concomitant renal impairment (see section "Dosage and administration").
Pediatric population
Children aged 4 to 12
Following single oral dose administration (20 mg/kg) in epileptic children (6 to 12 years of age), the half-life of levetiracetam was 6 hours. The apparent body weight adjusted clearance was approximately 30 % higher than in epileptic adults. Following repeated oral dose administration (20-60 mg/kg/day) in epileptic children (4 to 12 years of age), levetiracetam was rapidly absorbed. C_{max} was achieved 0.5-1 hour after dosing. C_{max} and the area under the concentration-time curve (AUC) increased in a linear, dose-dependent fashion. The elimination half-life was approximately 5 hours, the apparent total body clearance was 1.1 ml/min/kg.
Infants and children from 1 month to 4 years of age
Following single dose administration (20 mg/kg) of a 100 mg/ml oral solution in epileptic children (1 month to 4 years of age), levetiracetam was rapidly absorbed, C_{max} was achieved approximately 1 hour after administration of the drug. The pharmacokinetic results indicate that the half-life was shorter (5.3 h) than in adults (7.2 h), and the apparent clearance was faster (1.5 ml/min/kg) than in adults (0.96 ml/min/kg).
The results of another population pharmacokinetic analysis conducted in patients from 1 month to 16 years of age indicate that 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 in younger infants, and subsided as age increased, becoming negligible around 4 years of age.
Both population pharmacokinetic analyses indicate an increase of apparent clearance of levetiracetam by approximately 20 % upon concomitant administration with an enzyme-inducing anti-epileptic drug.

Clinical particulars.
Indications.
Monotherapy (first-choice drug) in the treatment of:
- partial seizures with or without secondary generalization in adults and adolescents from 16 years of age with newly diagnosed epilepsy.

As adjunctive therapy in the treatment of:
- partial seizures with or without secondary generalization in adults and children from 1 month of age with epilepsy;
- myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy;
- primary generalized tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalized epilepsy.

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

Interaction with other medicinal products and other forms of interaction.
Anti-epileptic medicinal products
Levetiracetam does not influence other anti-epileptic medicinal products (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and they, in their turn, do not influence the pharmacokinetics of levetiracetam.
As in adults, there is no evidence of clinically significant interaction of the medicinal product in pediatric patients receiving up to 60 mg/kg/day of levetiracetam.
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 anti-epileptic medicinal products. Dose adjustment is not required.
Probenecid
Probenecid (500 mg 4 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 concentrations of this metabolite remain 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 pharmacokinetic interactions with other medicinal products
Levetiracetam at a daily dose of 1000 mg does not influence the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel); endocrine parameters (luteinizing hormone and progesterone) were not modified. Levetiracetam at a daily dose of 2000 mg does not influence the pharmacokinetics of digoxin and warfarin; prothrombin time was 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 upon concomitant administration of osmotic laxative macrogol with oral levetiracetam. Therefore, macrogol should not be taken orally for one hour before and for one hour after taking levetiracetam.
Food and alcohol
The extent of absorption of levetiracetam is not altered by food, but the rate of absorption is slightly reduced if the drug is taken with food. No data on the interaction of levetiracetam with alcohol are available.

Administration details.
Renal impairment
Patients with renal impairment may require levetiracetam dose adjustment. In patients with severely impaired hepatic function, assessment of renal function is recommended before dose selection (see section “Dosage and administrations”).
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 significant weakness, fever, recurrent infections or coagulation disorders (see section "Adverse reactions").

Suicide

Suicide, suicide attempts, suicidal ideation and behavior 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 somewhat increased risk of suicidal thoughts and behavior. The mechanism of this risk is not known. Therefore, considering such a risk, patients should be monitored for signs of depression, suicidal ideation and behavior, and treatment should be adjusted if appropriate. Patients (and their caregivers) should be advised to report any signs of depression, suicidal ideation or behavior to their physician.

Abnormal and aggressive behavior

Levetiracetam may cause psychotic symptoms and behavioral abnormalities including irritability and aggressiveness. Patients treated with levetiracetam should be monitored for developing psychiatric signs, in particular significant mood and/or personality changes. If such behaviors emerge, treatment should be adjusted or gradual discontinuation of levetiracetam should be considered. If discontinuation is necessary, it should be done according to the recommendations described in section "Dosage and administration".

Worsening of seizures

As with other types of anti-epileptic drugs, levetiracetam may rarely exacerbate seizure frequency and 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.

Electrocardiogram QT interval prolongation

Rare cases of electrocardiogram QT interval prolongation have been reported during the post-marketing period. Levetiracetam should be used with caution in patients with long QT syndrome; upon concomitant treatment with drugs affecting the QT interval; in patients with relevant pre-existing cardiac disease or electrolyte disturbances.

Children

Available data regarding children did not suggest any impact on growth and puberty. However, long term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children remain unknown.

Excipients

The drug contains methylparaben (E 218) and propylparaben (E 216) which may cause allergic reactions (possibly delayed). The drug also contains liquid maltitol, therefore, patients with known intolerance to some sugars should consult the physician before taking this medicinal product.

This medicinal contains less than 1 mmol of sodium per dose, therefore is practically sodium-free.

Use during pregnancy or breastfeeding.

Women of childbearing age

Special recommendations should be given to women of childbearing age. Treatment with levetiracetam should be reviewed when a woman is planning a pregnancy. As with all anti-epileptic 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 anti-epileptic medicines could be associated with a higher risk of congenital malformations than monotherapy, depending on the combination of drugs.

Pregnancy

A large amount of postmarketing data on pregnant women taking levetiracetam (more than 1800 women, among which 1500 women used the drug during the I trimester) does not suggest an

increase in the risk of major congenital malformations. Only limited evidence is available on the development of the nervous system of children exposed to levetiracetam monotherapy *in utero*. However, current epidemiological studies (approximately 100 children) do not suggest an increased risk of neurodevelopmental disorders or delays. Levetiracetam can be used during pregnancy if it is considered clinically needed after careful assessment. In such case, the lowest effective dose is recommended. Physiological changes during pregnancy may affect levetiracetam concentrations. A decrease in levetiracetam plasma concentrations has been observed during pregnancy. This decrease is more pronounced during the III 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 benefits/risks of the treatment should be weighed considering the importance of breastfeeding.

Impact on fertility

No impact on animal fertility was detected. Potential risk for humans is unknown as there are no available clinical data.

Effect on reaction rate when driving motor transport or using other mechanisms.

Levetiracetam has minor or moderate influence on the ability to drive motor transport or use other mechanisms. Due to possible individual sensitivity, some patients might experience somnolence, dizziness and 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 skilled tasks, requiring boosting attention span, e.g. driving motor transport or using other mechanisms. Patients are advised not to drive vehicles and operate other mechanisms, until it is established that their ability to perform such activities is not affected.

Dosage and administration.

The drug may be taken with or without food. The oral solution may be taken after diluting it in a glass of water or baby's bottle. After oral administration the bitter taste of levetiracetam may be experienced.

Monotherapy

Adults and adolescents from 16 years of age

Monotherapy in adults and adolescents from 16 years of age is recommended to start with a dose 500 mg/day (250 mg twice daily). After 2 weeks, the dose may be increased to the initial therapeutic dose – 1000 mg/day (500 mg twice daily). The dose may be increased up to 250 mg twice daily every two weeks depending upon the clinical response. The maximum daily dose is 3000 mg/day (1500 mg twice daily).

Children and adolescents under 16

The safety and efficacy of levetiracetam in children and adolescents under 16 years of age as monotherapy treatment have not been established.

No data are available.

Add-on therapy

The physician should prescribe the most appropriate pharmaceutical form, method of administration and dosage according to age, body weight and dose.

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

The initial therapeutic dose is 1000 mg/day (500 mg twice daily). This dose may be started on the first day of treatment.

Depending upon the clinical response and tolerability, the daily dose may be increased up to 3000 mg/day (1500 mg twice daily). The dose may be increased or decreased by 1000 mg/day (500 mg twice daily) every two to four weeks.

Infants aged 6 to 23 months, children (2 to 11 years) and adolescents (12 to 17 years) weighing

less than 50 kg
The initial therapeutic dose is 10 mg/kg twice daily.
Depending upon the clinical response and tolerability, the dose can be increased up to 30 mg/kg twice daily. Dose changes should not exceed 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.

Table 1

Dose recommendations for infants from 6 months of age, children and adolescents

Body weight	Starting dose – 10 mg/kg twice daily	Maximum dose – 30 mg/kg twice daily
6 kg(1)	60 mg (0,6 ml) twice daily	180 mg (1,8 ml) 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	1500 mg twice daily

(1) Children 25 kg or less should preferably start the treatment with Logufen®, 100 mg/ml, oral solution.
(2) Dose in children 50 kg or more is the same as in adults.

Infants aged from 1 to <6 months
The initial therapeutic dose is 7 mg/kg twice daily.
Depending upon the clinical response and tolerability, the dose can be increased up to 21 mg/kg twice daily. Dose changes should not exceed increases or decreases of 7 mg/kg twice daily every two weeks. The lowest effective dose should be used.
Infants should start the treatment with Logufen®, 100 mg/ml, oral solution.

Table 2

Dose recommendations for infants aged from 1 to 6 months

Body weight	Starting dose – 7 mg/kg twice daily	Maximum dose – 21 mg/kg twice daily
4 kg	28 mg (0,3 ml) twice daily	84 mg (0,85 ml) twice daily
5 kg	35 mg (0,35 ml) twice daily	105 mg (1,05 ml) twice daily
7 kg	49 mg (0,5 ml) twice daily	147 mg (1,5 ml) twice daily

Special Populations
Elderly (≥ 65 years)
Adjustment of the dose is recommended in elderly patients with compromised renal function (see section “Patients with renal impairment” below).
Patients with renal impairment
The daily dose of Levetiracetam should be individualised.
For adult patients, refer to the following table 3 and adjust the dose as indicated. An estimate of the patient's creatinine clearance (CL_{cr}) in ml/min is needed to adjust the dose.
In adults and adolescents weighing 50 kg or more, the following formula may be used to calculate CL_{cr} in ml/min based on serum creatinine levels (mg/dl):

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

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

$$CL_{cr}\ (ml/min/1{,}73m^2) = \frac{CL_{cr}\ (ml/min)}{BSA\ patient\ (m^2)} \times 1{,}73.$$

Table 3

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

Severity of renal impairment	Creatinine clearance ($ml/min/1.73m^2$)	Dosage
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 1 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 m^2 may be estimated from serum creatinine (mg/dl) determination, for young adolescents, children and infants, using the following formula (Schwartz formula):

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

ks = 0.45 in Term infants to 1 year old; ks = 0.55 in Children to less than 13 years and in adolescent female; ks = 0.7 in adolescent male.

Table 4

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

Severity of renal impairment	Creatinine clearance (ml/min/1.73m2)	Dose and frequency [(1)]	
		Infants 1 to <6 months	Infants 6 to 23 months, children and adolescents weighing less than 50 kg
Normal renal function	≥ 80	7 to 21 mg/kg (0,07 to 0,21 ml/kg) twice daily	10 to 30 mg/kg (0,1 to 0,3 ml/kg) twice daily
Mild	50–79	7 to 14 mg/kg (0,07 to 0,14 ml/kg) twice daily	10 to 20 mg/kg (0,1 to 0,2 ml/kg) twice daily

Moderate	30–49	3,5 to 10,5 mg/kg (0,035 to 0,105 ml/kg) twice daily	5 to 15 mg/kg (0,05 to 0,15 ml/kg) twice daily
Severe	< 30	3,5 to 7 mg/kg (0,035 to 0,07 ml/kg) twice daily	5 to 10 mg/kg (0,05 to 0,1 ml/kg) twice daily
End-stage (renal disease patients undergoing dialysis)	–	7 to 14 mg/kg (0,07 to 0,14 ml/kg) once daily (2) (4)	10 to 20 mg/kg (0,1 to 0,2 ml/kg) once daily (3) (5)

(1)Logufen®, 100 mg/ml, 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 10.5 mg/kg (0.105 ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.
(3) A 15 mg/kg (0.15 ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.
(4) Following dialysis, a 3.5 to 7 mg/kg (0.035 to 0.07 ml/kg) supplemental dose is recommended.
(5) Following dialysis, a 5 to 10 mg/kg (0.05 to 0.1 ml/kg) supplemental dose is recommended.

Patients with hepatic impairment

No dose adjustment is needed in patients with mild and 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 in patients with the creatinine clearance of < 60 ml/min/1.73 m^2.

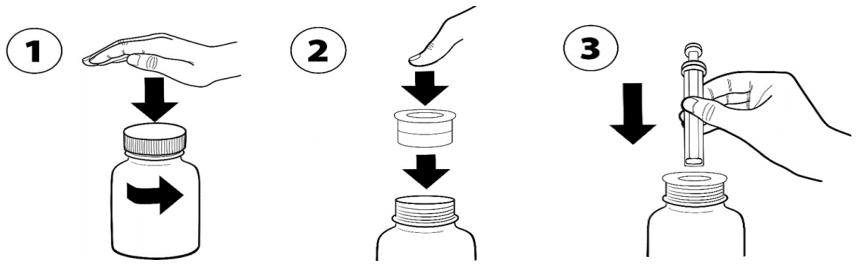
Children

The physician should prescribe the most appropriate pharmaceutical form, dosage and dosage form according to age, body weight and dose.
Logufen® , 100 mg/ml, oral solution is the preferred formulation for use in infants and children under the age of 6 years. In addition, available tablet dosages 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 these cases Logufen® , 100 mg/ml, oral solution should be used.

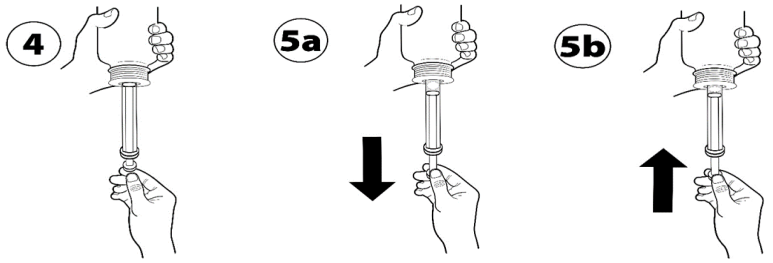
Method of administration of the oral solution

Dosing is carried out using measuring syringe that is included in the package. Syringe with a nominal capacity of 5 ml (corresponding to 500 mg of levetiracetam) graduated 0.1 ml (corresponding to 10 mg). The metered dose is diluted in a glass of water (200 ml) or in a baby's bottle.

Dosing of the solution using a measuring syringe:

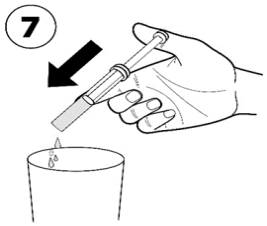


- Open a bottle (figure 1).
- When using for the first time, insert the adapter for the syringe into the neck of the bottle (figure 2).
- Insert the syringe into the adapter (figure 3).



- Turn the bottle upside down (figure 4).
- Draw a small amount of solution into the syringe by pulling the plunger down (figure 5a).
- Remove air bubbles by pressing the plunger (figure 5b).

- Fill the syringe with the solution by pulling the plunger to the mark corresponding to the required amount of solution in milliliters (ml) prescribed by the doctor (figure 5c).
- Turn the bottle upside down (figure 6a).
- Remove the syringe from the adapter (figure 6b).



- Inject the contents of the syringe into a glass of water or a baby bottle by pushing the plunger all the way down (рис. 7).
- If necessary, to achieve the required dose (see table 2), repeat the steps shown in the figures 3–7.
- Drink the entire contents of the baby glass/bottle.
- Close the bottle with a plastic cap (the syringe adapter remains in place).
- Rinse the syringe (disassembled) with water.

Treatment 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 infants older than 6 months, children and adolescents weighting less than 50 kg: dose decrease should not exceed 10 mg/kg twice daily every two weeks; in infants (less than 6 months): dose decrease should not exceed 7 mg/ kg twice daily every two weeks).

Children.

Logufen®, oral solution, may be prescribed to children from 1 month of age. The drug is not recommended to use in children under the age of 1 month due to the lack of data on the safety and

efficacy of such use. The safety of the drug in children and adolescents below 16 years as monotherapy treatment has not been established.

Overdose.
Symptoms
Somnolence, agitation, aggression, respiratory depression, depressed level of consciousness, coma were observed with levetiracetam overdoses.
Treatment
After an acute overdose, the stomach may be emptied by gastric lavage or by induction of emesis. There is no specific antidote. If necessary, carry out symptomatic treatment, including haemodialysis (is excreted up to 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 is based on summarized data analysis in 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 (adults and children) when using different approved epilepsy indications.
Adverse reactions reported in clinical studies (adults, adolescents, children and infants aged 1 month and over) and during post-marketing period, listed in the table 5 per System Organ Class and per frequency. The frequency is defined as follows: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10000, <1/1000) and very rare (<1/10000).

Table 5

MedDRA System Organ Classes	Frequency of adverse reactions			
	very common	common	uncommon	rare
Infections and infestations	Nasopharyngitis			Infections
Blood and lymphatic system disorders			Thrombocytopenia, leukopenia	Neutropenia, pancytopenia, agranulocytosis
Immune system disorders				Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), Hypersensitivity (including angioedema and anaphylaxis)
Metabolism and nutrition disorders		Anorexia	Body weight increase, body weight decrease	Hyponatraemia
Psychiatric disorders		Depression, hostility/ aggression, anxiety, insomnia,	Suicide attempt, suicidal ideation, psychotic	Suicide, personality disorder, thinking abnormal,

		nervousness/irritability	disorder, abnormal behaviour, hallucination, anger, confusional state, panic attack, affect lability/mood swings, agitation	delirium
Nervous system disorders	Somnolence, headache	Convulsion, balance disorder, dizziness, lethargy, tremor	Amnesia, memory impairment, ataxia, coordination abnormal, paraesthesia, disturbance in attention	Hyperkinesia, dyskinesia, choreoathetosis, gait disturbance, encephalopathy, seizures aggravated
Eye disorders			Diplopia, vision blurred	
Ear and labyrinth disorders		Vertigo		
Cardiac disorders				QT interval prolongation on the electrocardiogram
Respiratory, thoracic and mediastinal disorders		Cough		
Gastrointestinal disorders		Diarrhoea, dyspepsia, nausea, vomiting, abdominal pain		Pancreatitis
Hepatobiliary disorders			Liver function test abnormal	Hepatitis, hepatic failure
Renal and Urinary Disorders				Acute kidney injury
Skin and subcutaneous tissue disorders		Rash	Eczema, pruritus, alopecia	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme

Musculoskeletal and connective tissue disorders			Myalgia, muscular weakness	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.

Description of selected adverse reactions
The risk of anorexia is higher when levetiracetam is coadministered with topiramate. In several cases of alopecia, hair restoration was observed when levetiracetam was discontinued.
In several cases of pancytopenia, bone marrow depression was observed. Cases of encephalopathy generally occurred at the beginning of the treatment (few days to a few months) and were reversible after treatment discontinuation.
Children
The adverse reaction profile of levetiracetam is generally similar across different age groups and across the approved epilepsy indications. Safety results in children in placebo-controlled clinical studies were consistent with the safety profile of levetiracetam in adults, except for behavioural and psychiatric adverse reactions which were more common in children than in adults. In children and adolescents aged 4 to 16 years, vomiting (very common, 11.2%), agitation (common, 3.4%), mood swings (common, 2.1%), 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.

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. Healthcare professionals are asked to report any suspected adverse reactions to the State Enterprise "State Expert Center of MOH of Ukraine" and to the applicant via the feedback form at the website: https://kusum.ua/pharmacovigilance/.

Shelf-life.
2 years.

Storage conditions.
Store at a temperature not more than 25 °C in the original package.
Keep out of reach of children.
After the first opening of the bottle, store the drug for no more than 28 days.

Package.
200 ml are in a glass bottle with tamper evident cap; 200 ml are in a glass bottle with child proof cap. Each bottle is in a carton box with a 5 ml syringe dispenser and syringe adapter.

Conditions of supply.

Prescription only.

Manufacturer.
“KUSUM PHARM” LLC.

Address of manufacturer and manufacturing site.
40020, Ukraine, Sumy region, Sumy, Skryabina Str., 54.

or

Manufacturer.
LLC “GLADPHARM LLC”.

Address of manufacturer and manufacturing site.
40020, Ukraine, Sumy region, Sumy, Davydovskoho Hryhoriia Str., 54.

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