Med Choice™
CNS

300 mL

Levetiracetam

Kepdin®

100 mg / mL Oral Solution

ANTIEPILEPTIC

℞

PRODUCT DESCRIPTION:
A clear colorless to slightly yellowish oral solution with grape flavor and odor. It is packed in a wide mouth Boston Round Amber Bottle 300 mL with syringe in an individual box.

FORMULATION:
Each mL contains:
Levetiracetam.....100 mg

PHARMACOLOGIC / PHARMACODYNAMICS:
Pharmacotherapeutic group: antiepileptics, Anatomical Therapeutic Chemical (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 but appears to be different from the mechanisms of current antiepileptic medicinal products. In vitro and in vivo experiments suggest that levetiracetam does not alter basic cell characteristics and normal neurotransmission.
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.

PHARMACOKINETICS:
Levetiracetam is readily absorbed from the gastrointestinal tract with a bioavailability of almost 100%; peak plasma concentrations are usually achieved within 1.3 hours of oral doses and steady state achieved after 2 days. Plasma protein binding is minimal at less than 10%. Levetiracetam is not extensively metabolized; about 25% of a dose is metabolized by hydroxylation to inactive metabolites. Around 95% of a dose is excreted as unchanged drug and metabolites in the urine. The plasma elimination half-life has been reported to be about 7 hours in adults and children aged 12 years and over; the half-life may be shorter in younger children. Levetiracetam is distributed into breast milk.

INDICATION:
Levetiracetam is used as an adjunct in the treatment of partial seizure with or without secondary generalizations, myoclonic seizure and primary generalized tonic-clonic seizure.

DOSAGE AND ADMINISTRATION:
• Always take this medicine exactly as mentioned by the doctor. Ask the doctor for any uncertainty. Levetiracetam must be taken twice a day, once in the morning and once in the evening, at about the same time each day.

• It is used as an adjunct in the treatment of partial seizures with or without secondary generalizations in adults and children aged 4 years and over: in the UK, adults and adolescents aged 16 years and over may also be given levetiracetam as monotherapy for this indication. In addition, levetiracetam is licensed for adjunctive use in the treatment of myoclonic seizures in adults and children aged 12 years and over with juvenile myoclonic epilepsy. It is also licensed for use as an adjunct in the treatment of primary generalized tonic-clonic seizures in adults and children with idiopathic generalized epilepsy; for this indication, in the UK, licensed use is restricted to children aged 12 years and over, whereas in the USA, it is licensed from 6 years of age. The daily oral dose of levetiracetam is given in two divided doses.

• The initial adult dose when used as an adjunct is 1 g on the first day of treatment; thereafter, the daily dose may be increased in steps of 1 g every 2 to 4 weeks until effective antiepileptic control is achieved, up to a maximum dose of 3 g daily. The initial dose in children weighing less than 50 kg is 20 mg / kg daily which may be increased in steps of 20 mg / kg every 2 weeks to a maximum of 60 mg / kg daily.

• Children and adolescents weighing 50 kg or more should be given the usual adult dose (see above). When used as monotherapy, the initial dose of levetiracetam is 500 mg daily, increased after 2 weeks to 1 g daily. Further increases may be made in steps of 500 mg every 2 weeks up to a maximum of 3 g daily. When oral use is not feasible, levetiracetam may be given by intravenous infusion over 15 minutes in doses similar to those used orally; as with the oral formulation, details of licensed uses and ages may vary from country to country. UK licensed product information states that there has been no experience with the use of intravenous levetiracetam for more than 4 days. Reduced doses are recommended in renal and severe hepatic impairment (see below). As with other antiepileptics, withdrawal of levetiracetam therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. UK licensed product information recommends reducing the daily dose in adults by 1 g every 2 to 4 weeks; in children, the dose reduction should not exceed 20 mg / kg every 2 weeks.

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

Renal impairment
The daily dose must be individualized according to renal function (see Warning and Precaution)
For adult patient, refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance in mL/min is needed. The creatinine clearance 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:

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

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

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

CLcr = Creatinine Clearance

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

Group	Creatinine Clearance (mL/min/1.73 m²)	Dosage and frequency
Normal	>80	500 to 1500 mg (5 mL to 15 mL) twice daily
Mild	50 - 79	500 to 1000 mg (5 mL to 10 mL) twice daily
Moderate	30 - 49	250 to 750 mg (2.5 mL to 7.5 mL) twice daily
Severe	<30	250 to 500 mg (2.5 mL to 5 mL) twice daily
End-stage renal disease patient undergoing dialysis[1]	- - - -	500 to 1000 mg (5 mL to 10 mL) once daily[2]

[1] A 750 mg (7.5 mL) loading dose is recommended on the first day of treatment with levetiracetam.
[2] Following dialysis, a 250 to 500 mg (2.5 mL to 5 mL) 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 the study in adult renally impaired patients.
The CLcr 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)

$$\text{CLcr (mL /min /1.73 m}^2\text{)} = \frac{\text{Height (cm)} \times \text{ks}}{\text{serum creatinine (mg/dL)}}$$

ks = 0.55 in Children 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/1.73 m²)	Dosage and frequency[1] • 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 patient undergoing dialysis	- - - -	10 to 20 mg / kg (0.10 to 0.20 mL / kg) once daily[2,3]

[1] Levetiracetam oral solution should be used for doses under 250 mg 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 patient 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/1.73 m².

DIRECTION FOR USE:
Using oral syringe, aspirate the liquid according on the required mL or dosage prescribed by your doctor. Can be taken with or without food.

CONTRAINDICATION / PRECAUTION / WARNING:
Take special care with upon taking this medicine.
• Hypersensitivity to levetiracetam or other pyrrolidone derivatives or any of the excipients.
• If you suffer from kidney problems, follow your doctor's instructions. He/she may decide if your dose should be adjusted.
• If you notice any slowdown in the growth or unexpected puberty development of your child, please contact your doctor.
• If you notice an increase in seizure severity (e.g. increase number), please contact your doctor.
• A small number of people being treated with anti-epileptics such as levetiracetam oral solution have had thoughts of harming or killing themselves. If you have any symptoms of depression and/or suicidal ideation, please contact your doctor.

Discontinuation
• In accordance with current clinical practice, 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 weighing 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).
Renal insufficiency
• 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.
Suicide
• Suicide, suicide attempt, 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 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.
Pediatric population
• 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.
• The safety and efficacy of levetiracetam has not been thoroughly assessed in infants with epilepsy aged less than 1 year. Only 35 infants aged less than 1 year with partial onset seizures have been exposed in clinical studies of which only 13 were aged < 6 months.
Excipients
• Levetiracetam 100 mg / mL oral solution includes methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) which may cause allergic reactions (possibly delayed).
Do not take this medicine if any of the above applies to you. If you are not sure, talk to your doctor or health care provider.

PREGNANCY AND LACTATION:
Pregnancy
There are no adequate data available from the use of levetiracetam in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for human is unknown. Levetiracetam is not recommended during pregnancy and in women of childbearing potential not using contraception unless clearly necessary. As with other antiepileptic medicinal products, 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. Discontinuation of antiepileptic treatments may result in exacerbation of the disease which could be harmful to the mother and the fetus.

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.

DRUG INTERACTION:
Antiepileptic medicinal products
Pre-marketing data from clinical studies conducted in adults indicate that levetiracetam did not influence the serum concentrations of existing antiepileptic medicinal products (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin, and primidone) and that these antiepileptic medicinal products did not influence the pharmacokinetics of levetiracetam.
As in adults, there is no evidence of clinically significant medicinal product interactions in 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. It is expected that other medicinal products excreted by active tubular secretion could also reduce the renal clearance of the metabolite. The effect of levetiracetam on probenecid was not studied and the effect of levetiracetam on other actively secreted medicinal products, e.g. NSAIDs, sulfonamides and methotrexate, is unknown.
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 (luteinizing 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. Co-administration with digoxin, oral contraceptives, and warfarin did not influence the pharmacokinetics of levetiracetam.
Antacids
No data on the influence of antacids on the absorption of levetiracetam are available.

ADVERSE DRUG REACTION:
• Call your healthcare provider right away if you have any of the following symptoms: mood and behavior changes such as aggression, agitation, anger, anxiety, apathy, mood swings, depression, hostility, and irritability. A few people may get psychotic symptoms such as hallucinations (seeing or hearing things that are really not there), delusions (false or strange thoughts or beliefs) and unusual behavior, extreme sleepiness, tiredness, and weakness, problems with muscle coordination (problems walking and moving).
• The most common side effects seen in people who take levetiracetam oral solution include: sleepiness, weakness, dizziness, infection.
• The most common side effects seen in children who take levetiracetam oral solution include, in addition to those listed above: accidental injury, irritability, hostility.
• These side effects can happen at any time but happen more often within the first 4 weeks of treatment except for infection.
• Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of levetiracetam oral solution. For more information, ask your healthcare provider or pharmacist.

OVERDOSE AND TREATMENT:
Symptoms
Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression, 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. Treatment of an overdose will be symptomatic and may include hemodialysis. The dialyzer extraction efficiency is 60% for levetiracetam and 74% for the primary metabolite.

STORAGE CONDITION:
Store at temperatures not exceeding 30°C.

DOSAGE FORM AND PACKING AVAILABLE:
Levetiracetam (Kepdin) Oral Solution is available in bottles of 300 mL packed in commercial box.

INSTRUCTION AND SPECIAL PRECAUTION FOR HANDLING AND DISPOSAL:
No special requirements for disposal. Any unused product should be disposed of in accordance with local requirements.

"For suspected adverse drug reaction, report to FDA: www.fda.gov.ph. Seek medical attention immediately at the first sign of any adverse drug reaction."

CAUTION STATEMENT:
Foods, Drugs, Devices, and Cosmetics act prohibits dispensing without prescription.
Keep this product out of reach of children.

REGISTRATION NUMBER: DRP-12346
DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION: 21 JULY 2022
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