Front Side

210 mm

Levetiracetam

Levacetam

250 mg Film-Coated Tablet
500 mg Film-Coated Tablet
Antiepileptic

FORMULATION:
Each film-coated tablet contains: Levetiracetam USP…..... 250 mg
Each film-coated tablet contains: Levetiracetam USP…..... 500 mg

DESCRIPTION:
250 mg: Blue colored, circular, biconvex film-coated tablets, plain on both surfaces with mottled appearance.
500 mg: Blue colored, oblong shaped film-coated tablets with a break line on one surface and plain on the other with mottled appearance.

PHARMACOLOGY:
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 medicinal product.

PHARMACOKINETICS:
Absorption of levetiracetam is rapid, with peak plasma concentrations occurring in about an hour following oral administration. The oral bioavailability of levetiracetam tablets is 100%. Food does not affect the extent of absorption of levetiracetam but it decreases C_{max} by 20% and delays T_{max} by 1.5 hours. Levetiracetam and its major metabolite are less than 10% bound to plasma proteins; clinically significant interactions with other drugs through competition for protein binding sites are therefore unlikely. Levetiracetam is not extensively metabolized in humans. The major metabolic pathway is the enzymatic hydrolysis of the acetamide group, which produces the carboxylic acid metabolite, ucb L057 (24% of dose) and is not dependent on any liver cytochrome P450 isoenzymes. Levetiracetam plasma half-life in adults is 7 ± 1 hour. Levetiracetam is eliminated from the systemic circulation by renal excretion as unchanged drug which represents 66% of administered dose. The total body clearance is 0.96 mL/min/kg and the renal clearance is 0.6 mL/min/kg.

INDICATIONS:
Levetiracetam is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalization 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 generalization in adults and children from one month 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 generalized tonic-clonic seizures in adults and adolescents from 6 years of age with Idiopathic Generalized Epilepsy.

CONTRAINDICATIONS:
Levetiracetam is contraindicated in patients with known hypersensitivity to the active substance or other pyrrolidone derivatives or to any of the excipients.

ADVERSE EFFECTS:
The adverse events reported with the use of levetiracetam are infection, nasopharyngitis, thrombocytopenia, leukopenia, neutropenia, pancytopenia, anorexia, weight increase, weight loss, agitation, depression, emotional lability/mood swings, hostility/aggression, insomnia, nervousness/irritability, personality disorders, abnormal thinking, abnormal behavior, anger, somnolence, amnesia, ataxia, convulsion, dizziness, headache, hyperkinesia, tremor, balance disorder, diplopia, vision blurred, vertigo, cough increased, abdominal pain, diarrhea, dyspepsia, nausea, vomiting, hepatic failure, hepatitis, abnormal liver function test, rash, eczema, pruritus, etc.
For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph Patient should seek medical attention immediately at the first sign of any adverse drug reaction.

WARNINGS AND PRECAUTIONS:
Serious Dermatological Reactions
Serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in both children and adults treated with levetiracetam. The median time of onset is reported to be 14 to 17 days, but cases have been reported at least four months after initiation of treatment. Recurrence of the serious skin reactions following rechallenge with levetiracetam has also been reported. If signs and symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered.

Seizure Control During Pregnancy
Physiological changes may gradually decrease plasma level of levetiracetam throughout pregnancy. This decrease is more pronounced during the third trimester. It is recommended that patients be monitored carefully during pregnancy. Close monitoring should continue through the postpartum period especially if the dose was changed during pregnancy.

DRUG INTERACTIONS:
Levetiracetam did not influence the serum concentrations of existing anti-epileptic medicinal products (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these anti-epileptic medicinal products did not influence the pharmacokinetics of levetiracetam. 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. Levetiracetam 1000 mg daily did not influence the pharmacokinetics of oral contraceptives (ethinyl-estradiol 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 were not modified. Co-administration with digoxin, oral contraceptives and warfarin did not influence the pharmacokinetics of levetiracetam. The extent of absorption of levetiracetam was not altered by food, but the rate of absorption was slightly reduced.

SPECIAL POPULATION:
Pregnancy and Lactation
Pregnancy Category C
There are no adequate and well-controlled studies in pregnant women. In animal studies, levetiracetam produced evidence of developmental toxicity, including teratogenic effects, at doses similar to or greater than human therapeutic doses. Drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Levetiracetam is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.
Pediatric Use
The safety and effectiveness in the adjunctive treatment of partial onset seizures in pediatric patients age 1 month to 16 years old with epilepsy have been established. The dosing recommendation in these pediatric patients varies according to age group and is weight-based.

240 mm

35 mm | 35 mm | 35 mm | 35 mm | 35 mm | 35 mm

PHARMACODE READING DIRECTION

14 (L) x 8 (H) mm

PHARMACODE READING DIRECTION

326

Back Side

210 mm

The safety and effectiveness as adjunctive treatment of myoclonic seizures in adolescents 12 years of age and older with juvenile myoclonic epilepsy have been established.
The safety and effectiveness as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in pediatric patients 6 years of age and older with idiopathic generalized epilepsy have been established.

Geriatric Use
Levetiracetam is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function.
Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Renal Impairment
Clearance of levetiracetam is decreased in patients with renal impairment and is correlated with creatinine clearance. Dose adjustment is recommended for patients with impaired renal function and supplemental doses should be given to patients after dialysis.

DOSAGE AND ADMINISTRATION:
Partial onset seizures
- Pediatric patients weighing 20 to 40 kg, treatment should be initiated with a daily dose of 500 mg given as twice daily dosing (250 mg twice daily). The daily dose should be increased every 2 weeks by increments of 500 mg to a maximum recommended daily dose of 1500 mg (750 mg twice daily).
- Pediatric patients weighing more than 40 kg, treatment should be initiated with a daily dose of 1000 mg/day given as twice daily dosing (500 mg twice daily). The daily dose should be increased every 2 weeks by increments of 1000 mg/day to a maximum recommended daily dose of 3000 mg (1500 mg twice daily).
- Adults 16 years and older: 500 mg twice daily, increase as needed and tolerated in increments of 500 mg twice daily every 2 weeks to a maximum recommended dose of 1500 mg twice daily.

Myoclonic Seizures in Adults and Pediatric Patients 12 Years and Older
- Treatment should be initiated with a dose of 1000 mg/day, given as twice-daily dosing (500 mg twice daily). Dosage should be increased by 1000 mg/day every two weeks to the recommended daily dose of 3000 mg. The effectiveness of doses lower than 3000 mg/day has not been studied.

Primary Generalized Tonic-Clonic Seizures
- 6 years to < 16 years: 10 mg/kg twice daily, increase in increments of 10 mg/kg twice daily every 2 weeks to recommended dose of 30 mg/kg twice daily.
- Adults 16 years and older: 500 mg twice daily, increase by 500 mg twice daily every 2 weeks to recommended dose of 1500 mg twice daily.

Adult Patients with Impaired Renal Function
- Dose adjustment is recommended, based on the patient's estimated creatinine clearance

Table 1: Dosing Adjustment Regimen for Adult Patients with Impaired Renal Function

Group	Creatinine Clearance Frequency (mL/min/1.73m^2)	Dosage (mg)	
Normal	>80	500 to 1,500	Every 12 hours
Mild	50-80	500-1,000	Every 12 hours
Moderate	30-50	500-1,000	Every 12 hours
Severe	<30	250-500	Every 12 hours
ESRD Patients	------	500-1,000[1]	Every 24 hours[1]

[1]Following dialysis, a 250 to 500 mg supplemental dose is recommended.

OVERDOSAGE, SYMPTOMS AND ANTIDOTE:
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 dialyser extraction efficiency is 60% for levetiracetam and 74% for the primary metabolite.

STORAGE:
Store at temperatures not exceeding 30°C.

CAUTION:
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY:
Levetiracetam (Levacetam) 250 mg film-coated tablet in Alu/Clear PVC Blister Pack x 10's (Box of 30's & 100's)
Levetiracetam (Levacetam) 500 mg film-coated tablet in Alu/Clear PVC Blister Pack x 10's (Box of 30's & 100's)

REGISTRATION NO.:
Levetiracetam (Levacetam) 250 mg film-coated tablet: DRP-7249-01
Levetiracetam (Levacetam) 500 mg film-coated tablet: DRP-7248-01

DATE OF FIRST AUTHORIZATION:
Levetiracetam (Levacetam) 250 mg film-coated tablet: 21 January 2016
Levetiracetam (Levacetam) 500 mg film-coated tablet: 22 April 2016

DATE OF REVISION OF PACKAGE INSERT:
December 2020

Manufactured by :
Micro Labs Limited
92, Sipcot Industrial Complex,
Hosur - 635 126, Tamil Nadu, India
Imported by:
OEP PHILIPPINES, INC.
Unit 606, 6/F SEDCCO I Bldg., cor. Rada &
Legaspi Sts., Legaspi Village, Makati City 1229
Distributed by:
BROWN AND BURK PHILIPPINES,INC
Unit 501, 5/F SEDCCO I Bldg., 120 Rada cor.
Legaspi Sts., Legaspi Village, Makati City 1229

EXG-ML01I-1814

240 mm

35 mm | 35 mm | 35 mm | 35 mm | 35 mm | 35 mm

Paper 35 to 60 gsm

Size : 210 (L) x 240 (H) mm
Drg. No.: W0990005916Z-000
Folding size: 35 x 120 mm
Carton size: 43 x 32 x 90 mm
60 x 25 x 85 mm

MICRO LABS LIMITED, BANGALORE, INDIA			
1	Product Name	Levacetam	Colours Used
2	Strength	250 mg and 500 mg	■ BLACK
3	Component	Leaflet	
4	Category	Export - Philippines	
5	Dimension	210 (L) x 240 (H) mm	
6	Artwork Code	EXG-ML01I-1814	
7	Pharma Code	326	
8	Reason for Change	New Artwork	

	Prepared by (DTP)	Checked by (PD)	Approved by			
			Head CQA	Head Production/ Packing (Site)	Head QC (Site)	Head QA (Site)
Sign	Kantharaju L.					
Date	18-11-2022					