เอกสารกำกับยาภาษาอังกฤษ

EPITAM 500

1. Product Name

EPITAM 500

2. Name and strength of active ingredient

Each film-coated tablet contains Levetiracetam 500 mg

3. Product description

Yellow, oval, biconvex film-coated tablet. One side has incision, letter “L” and “T” on each side. Another side has the figure “500”

4. Pharmacodynamic/Pharmacokinetics

4.1 Pharmacodynamic

Mechanism of action

Levetiracetam, a pyrrolidine derivative, is an anticonvulsant agent that is structurally unrelated to other currently available anticonvulsants. The mechanism of anticonvulsants action of levetiracetam is unknown.[1]

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 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. 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.[2]

4.2 Pharmacokinetics

Levetiracetam is readily absorbed from the gastrointestinal tract with a bioavailability of almost 100%, peak plasma concentrations usually occur within 1.3 hours of oral doses and steady state after 2 days. Plasma protein binding is minimal at less than 10%. Levetiracetam is not extensively metabolised; about 25% of a dose is metabolised 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.[3]

5. Indication

Levetiracetam is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalization in adults and adolescents from 16 years of age with newly diagnosed epilepsy. [2]

Levetiracetam is indication as adjunctive therapy in the treatment of:

- partial onset seizures with or without secondary generalization in adults, adolescents and children from 4 years of age with epilepsy. [2]
- myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy. [2, 4]
- primary generalized tonic-clonic seizures in adults, adolescents and children from 6 years of age with idiopathic generalized epilepsy. [2, 4]

6. Recommended Dose [2]

- **Adult:**

Monotherapy

Adults and adolescents from 16 years of age

The recommended starting dose is 250 mg twice daily which should be increased to an initial therapeutic dose of 500 mg twice daily after 2 weeks. The dose can be further increased by 250 mg twice daily every two weeks depending upon the clinical response. The maximum dose is 1,500 mg twice daily.

Add-on therapy

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

The initial therapeutic dose is 500 mg twice daily. This dose can be started on the first day of treatment. Depending upon the clinical response and tolerance, the daily dose can be increased up to 1,500 mg twice daily. Dose changes can be made in 500 mg twice daily increases every two to four weeks.

- **Children:**

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

The tablet formulation is not adapted for use in children under the age of 6 years. Levetiracetam oral solution is preferred formulation for use in this population.

In additional, the available dose strengths of the tablets are not appropriate for initial treatment in children weighing less than 25 kg, for patients unable to swallow tablets or for the administration of doses below 250 mg. In all of the above cases levetiracetam oral solution should be used.

Monotherapy

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

There are no data available.

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

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

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

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

Depending upon the clinical response and tolerability, the dose can be increased up to 30 mg/kg twice daily.

Dose changes should not exceed increments or decrements of 10 mg/kg twice daily every two weeks. The lowest effective dose should be used.

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

Dose recommendations for children and adolescents:

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

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

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

Adequate presentation must be used to ensure the accuracy of the dosing.

- **Elderly:**

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

- **Renal impairment:**

The daily dose must be individualised according to renal function.

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 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:

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

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

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

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

Group	Creatinine clearance (ml/min/1.73 m^2)	Dosage and frequency
Normal	>80	500 to 1,500 mg twice daily
Mild	50-79	500 to 1,000 mg twice daily
Moderate	30-48	250 to 750 mg twice daily
Severe	<30	250 to 500 mg twice daily
End-stage renal disease patients undergoing dialysis[1]	-	500 to 1,000 mg once daily[2]

[1] A 750 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 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 adult and adolescent patients weighing less than 50 kg with impaired renal function

Group	Creatinine clearance (ml/min/1.73 m^2)	Dose 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	30-48	5 to 15 mg/kg (0.05 to 0.15 ml/kg) twice daily
Severe	<30	5 to 10 mg/kg (0.05 to 0.10 ml/kg) twice daily
End-stage renal disease patients undergoing dialysis	-	10 to 20 mg/kg (0.10 to 0.20 ml/kg) once daily[(*)(**)]

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

[(*)] A 15 mg/kg (015 ml/mg) loading dose is recommended on the first day of treatment with levetiracetam.

[(**)] Following dialysis, a 5 to 10 mg/kg (0.05 to 0.10 ml/kg) supplemental dose is recommended.

- **Hepatic impairment:**

No dose adjustment is needed in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the creatinine clearance may underestimate the renal insufficiency. Therefore a 50% reduction of the daily maintenance dose is recommended when the creatinine clearance is < 60 ml/min/1.73 m^2.

7. Mode of Administration

EPITAM 500 is administered orally without regard to food. [1, 4]

8. Contraindication

- Levetiracetam is contraindicated in patients with known hypersensitivity to the drug or other pyrrolidone derivatives.[1, 2]

9. Warning and Precaution

1) Psychiatric symptoms: Psychosis, paranoia, hallucinations and behavioral symptoms (including aggression, agitation, anger, anxiety, apathy, confusion, depersonalization, depression, emotional lability, hostility, hyperkinesias, irritability, nervousness, neurosis, and personality disorder) may occur; dose reduction or discontinuation may be required.[4]

2) Suicidal ideation: Pooled analysis of trials involving various antiepileptics (regardless of indication) showed an increased risk of suicidal thoughts/behavior (incidence rate: 0.43% treated patients compared to 0.24% of patients receiving placebo); risk observed as early as 1 week after initiation and continued through duration of trials (most trials 24 weeks or less). Monitor all patients for notable

changes in behavior that might indicate suicidal thoughts or depression; notify health care provider immediately if symptoms occur.[4]

3) Withdrawal: Anticonvulsants should not be discontinued abruptly of the possibility of increasing seizure frequency; therapy should be withdrawn gradually to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal.[4]

4) Renal function impairment: Use caution with renal impairment; dosage adjustment may be necessary. In patients with end-stage renal disease requiring hemodialysis, it is recommended that immediate-release formulations be used instead of extended-release formulations.[4]

5) Hematologic effects: Decreases in red blood cell counts, hemoglobin, hematocrit, white blood cell counts and neutrophils have been observed. Case of eosinophilia, agranulocytosis, and lymphocytosis have also been reported.[4]

10. Interactions with Other Medication [1]

1) Concomitant use of levetiracetam and other anticonvulsants (e.g., carbamazepine, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone, valproic acid) does not appear to affect the pharmacokinetics of levetiracetam.

2) Concomitant use of levetiracetam and digoxin does not appear to affect the pharmacokinetics or pharmacodynamics (e.g., cardiac rhythm effects) of digoxin; digoxin also does not affect the pharmacokinetics of levetiracetam.

3) Concomitant use of levetiracetam and oral contraceptives does not appear to affect the pharmacokinetics of oral contraceptives.

4) Concomitant use of levetiracetam and probenecid does not effect on levetiracetam pharmacokinetics was observed, but steady-state plasma concentrations of the principal inactive metabolite were approximately doubled due to a 60% reduction in renal clearance.

5) Concomitant use of levetiracetam and warfarin does not appear to affect the pharmacokinetics or pharmacodynamics (e.g., prothrombin time) of warfarin; warfarin also does not affect the pharmacokinetics of levetiracetam.

11. Pregnancy and Lactation

Pregnancy: Category C

Adverse events have been observed in animal reproduction studies. Levetiracetam crosses the placenta and can be detected in the neonate at birth. Concentrations in the umbilical cord at delivery are similar to those in the maternal plasma. Serum concentrations of levetiracetam may decreased as pregnancy progress; monitor carefully throughout pregnancy and postpartum.[4]

Lactation: levetiracetam is distributed into milk. Because of the potential for serious adverse reactions to levetiracetam in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the woman.[1]

12. Undesirable Effects [5]

Common

Gastrointestinal: loss of appetite (3% to 8%), vomiting (15%)

Immunologic: infectious disease (13%)

Musculoskeletal: decreased bone mineral density (70%), neck pain (2% to 8%)

Neurologic: asthenia (15%), dizziness (5% to 9%), headache (14% to 19%)

Psychiatric: abnormal behavior (7% to 37.6%), irritability (6% to 12%)

Respiratory: cough (2% to 9%), nasopharyngitis (7% to 15%)

Other: fatigue (10% to 11%)

Serious

Dermatologic: Stevens-Johnson syndrome, toxic epidermal necrolysis

Hematologic: decreased erythrocyte production, decreased white blood cell count (2.4% to 3.2%), eosinophil count raised (8.6%), neutropenia (2.4%), pancytopenia, thrombocytopenia

Hepatic: liver failure

Immunologic: anaphylaxis

Neurologic: somnolence (8% to 45%)

Psychiatric: suicidal intent (0.5%), suicide

Other: Angioedema

13. Overdose and Treatment [2]

Symptom and signs: somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with levetiracetam overdoses.

Treatment: There is no specific antidote for levetiracetam. Treatment of an overdose will be symptomatic and may include heamodialysis. The dialyser extraction efficiency is 60% for levetiracetam and 74% for the primary metabolite. Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

14. Storage Condition

Store below 30 °C [7]

15. Dosage Forms and Packaging Available

Dosage forms: Film-coated tablets

Packaging Available: 10 tablets in PVDC-Aluminium blister pack, which packed in carton box of 6, 10, 50 blisters.

16. Name and Address of Manufacturer

COMMUNITY PHARMACY PUBLIC COMPANY LIMITED

1 Soi Khubon 11, Ramintra, Kannayao, Bangkok 10230 Thailand

Tel. 0-2943-0935-7 Fax. 0-2510-7874

17. Date of revision of package insert

December 7th, 2023