ฉบับใหม่

**เอกสารกำกับยาภาษาอังกฤษ**

ข้อความเหมือนกันทุกขนาดบรรจุ

1. **Product Name:** Letta 500, Letta 250
2. **Name and Strength of Active Ingredient (S):** Each film-coated tablet contains
   - Letta 500 : Levetiracetam 500 mg
   - Letta 250 : Levetiracetam 250 mg
3. **Product Description:**
   - Letta 500 : Yellow, oblong, biconvex film coated tablet with “MCP” engraved on one side and plain on the other side.
   - Letta 250 : Blue, oblong, biconvex film coated tablet with “MCP” engraved on one side and plain on the other side.
4. **Pharmacodynamics / Pharmacokinetics:**

   *Pharmacodynamics*

   The mechanism of action of levetiracetam still remains to be fully elucidated but appears to be different from the mechanism of current antiepileptic medicinal products. *In vitro* and *in vivo* experiments suggest that levetiracetam does not alter basic cell characteristic and normal neurotransmission. Levetiracetam inhibits burst firing without affecting normal neuronal excitability, suggesting that levetiracetam may selectively prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity.

   *Pharmacokinetics*

   - **Absorption:** Rapid and almost complete. Oral bioavailability of levetiracetam is 100%, and is not affected by food. In fasted subject, peak plasma concentrations occurring in about 1 hour.
   - **Distribution:** Levetiracetam and its major metabolite are less than 10% bound to plasma proteins. The volume of distribution of levetiracetam is approximately 0.5 – 0.7 l/kg, a value close to the total body water volume.

- **Metabolism**: Levetiracetam is not extensively metabolized. The major metabolic pathway is the enzymatic hydrolysis of the acetamide group, which produces the carboxylic acid metabolite ucb L057(24% of the dose) and is not dependent on any liver cytochrome P450 (CYP-450) isoenzymes.
- **Excretion**: Levetiracetam plasma half-life in adults is 7±1 hour and is eliminated from the systemic circulation by renal excretion as unchanged drug, which represents 66% of the administered dose. The total body clearance is 0.96 ml/min/kg, and the renal clearance is 0.6 ml/min/kg. The mechanism of excretion is glomerular filtration with subsequent partial tubular reabsorption. The metabolite ucb L057 is excreted by glomerular filtration and active tubular secretion with a renal clearance of 4 ml/min/kg. Levetiracetam clearance and elimination are correlated to CrCl.

5. **Indications**:

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.

Levetiracetam is indicated 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.
- myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy.
- primary generalised tonic-clonic seizures in adults and children from 6 years of age with idiopathic generalised epilepsy.

6. **Recommended Dose:**

**Dosage** Levetiracetam tablets must be taken orally and may be taken with or without food. The daily dose is administered in two equally divided doses.

*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 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 or decreases every two to four weeks.

**Special Populations**

**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 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. 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.

*Add-on therapy*

Children (4 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 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: | Maximum dose: |
|---|---|---|
| 25 kg | 250 mg twice daily | 750 mg twice daily |
| From 50 kg* | 500 mg twice daily | 1,500 mg twice daily |

* 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 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 (CrCl) in ml/min is needed. The CrCl 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:

$$\text{CrCl (ml/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} \text{ (x 0.85 for female)}$$

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

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

**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 - 1500 mg twice daily |
| Mild | 50 - 79 | 500 - 1000 mg twice daily |
| Morderate | 30 - 49 | 250 - 750 mg twice daily |
| Severe | < 30 | 250 - 500 mg twice daily |
| End-stage renal disease patients undergoing dialysis[1] | - | 500 - 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 supplement 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 CrCl 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):

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

ks = 0.55 in Children to less than 13 years and in adolescents female; ks = 0.7 in adolescents male

**Dosing adjustment for children and adolescent patients weighing less than 50 kg with impairment renal function**

| Group | Creatinine clearance (ml/min/1.73 $m^2$) | Dosage and frequency |
|---|---|---|
| Normal | > 80 | 10 - 30 mg/kg (0.10 - 0.30 ml/kg) twice daily |
| Mild | 50 - 79 | 10 - 20 mg/kg (0.10 - 0.20 ml/kg) twice daily |
| Moderate | 30 - 49 | 5 - 15 mg/kg (0.05 - 0.15 ml/kg) twice daily |
| Severe | < 30 | 5 - 10 mg/kg (0.05 - 0.10 ml/kg) twice daily |
| End-stage renal disease patients undergoing dialysis | - | 10 - 20 mg/kg (0.10 - 0.20 ml/kg) once daily(*) (**) |

Levetiracetam oral solution should be used for doses under 250 mg and for patients unable to swallow tablets

(*) A 15 mg/kg (0.15 ml/kg) 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) supplement 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 $m^2$

**Discontinuation of therapy** Levetiracetam therapy should not be discontinued abruptly and should be withdrawn gradually by reducing the dosage by 1000 mg daily at 2-week intervals.

7. **Mode of Administration:**

Levetiracetam tablets are administered orally twice daily without regard to meals. Only administer as whole tablet.

8. **Contraindication:**

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

9. Precautions:
    - **CNS effects** In some patients, levetiracetam causes behavioral abnormalities, increase risk of suicidal thought or behavior. In addition, coordination difficulties, somnolence and asthenia occurred most frequently within the first 4 weeks of treatment.
    - **Dermatological effects** Serious dermatological reactions, including Stevens-Johnson syndrome and Toxic epidermal necrolysis (TEN), have been reported in both children and adult.
    - **Withdrawal seizures** Withdraw anticonvulsants, including levetiracetam gradually to minimize the potential of increased seizure frequency.
    - **Hematologic effects** Minor decreases in total mean erythrocyte count, mean hemoglobin, and mean hematocrit have been reported. Leukopenia, neutropenia, pancytopenia and thrombocytopenia also have been observed, although a causal relationship to the drug has not been established.
    - **Blood pressure effects** Increase in diastolic blood pressure in patients 1 month to younger than 4 years.
    - **Hazardous tasks** Advise patients not to drive or operate machinery or engage in other hazardous activities.
10. Warnings:
    1. This medicine may make patients feel asleep. Should not to drive or operate machinery or engage in other hazardous activities and do not take this medicine with alcohol drinks or any beverage which contains alcohol.
    2. This medicine may cause hematologic disorder.
    3. It is contraindicated in pregnancy women because it may cause birth defect.
    4. Should be use with caution in patients with hepatic and/or renal impairment.

11. **Interactions with Other Medicaments:**

- **Antiepileptic drugs** Clinically important pharmacokinetic interaction unlikely with anticonvulsants (e.g., carbamazepine, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone, valproic acid) and that these antiepileptic drugs did not influence the pharmacokinetics of levetiracetam. In pediatric patients, approximately 22% increase in levetiracetam clearance observed when concurrently administered with hepatic enzyme-inducing anticonvulsants; dosage adjustment not recommended. Levetiracetam did not alter plasma concentrations of carbamazepine, lamotrigine, topiramate or valproic acid in pediatric patients with epilepsy.
- **Probenecid** Probenecid (a renal tubular secretion blocking agent), has been shown to inhibit the renal clearance of the primary metabolite however; no effect on levetiracetam pharmacokinetics, but steady-state plasma concentrations of principal inactive metabolite were approximately doubled due to 60% reduction in renal clearance; clinically unimportant.
- **Oral contraceptives, digoxin and warfarin** Pharmacokinetic interaction unlikely.
- **Food** Food may delay, but does not affect the extent of absorption

12. **Pregnancy and Lactation:**

*Pregnancy:* Pregnancy category C.

There are no adequate and well-controlled studies in pregnant women. Use levetiracetam during pregnancy only if the potential benefit justifies the potential risk to the fetus. Although confirmation is needed, severe growth restriction has been observed in limited human pregnancy experience. It is not known if levetiracetam crosses the placenta. However, exposure to the embryo and fetus is expected because levetiracetam is low molecular weight (about 170) and lack of protein binding. It is not

known if levetiracetam causes folic acid deficiency, but it will usually be combined with other anticonvulsants, some of which may cause folic acid deficiency. Therefore, daily supplementation with 4 to 5 mg of folic acid combined with multivitamins that include adequate amounts of other B vitamins is recommended. As with other AEDs, physiological changes may gradually decrease plasma levels of levetiracetam throughout pregnancy. This decrease is more pronounced during the third trimester. It is recommended that patients be monitored carefully during pregnancy. The postpartum period especially if the dose was changed during pregnancy.

*Lactation:*

Levetiracetam is distributed into milk. Because of the potential for serious adverse reaction 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.

13. Undesirable Effects:

Common adverse effects occurring in 1% or more of patients receiving oral levetiracetam and more frequently than placebo include somnolence, asthenia, headache, infection, dizziness, pain, pharyngitis, depression, nervousness, rhinitis, anorexia, ataxia, vertigo, amnesia, anxiety, emotional lability, hostility, paresthesia, increased cough, sinusitis, and diplopia and were reported in clinical studies in which levetiracetam was administered in conjunction with other anticonvulsants. Asthenia, somnolence, and dizziness occurred predominantly during the initial 4 weeks of treatment.

14. Overdose and Treatment:

*Symptoms*

Aggression, agitation, coma, depressed level of consciousness, respiratory depression and somnolence.

*Treatment*

There is no specific antidote for levetiracetam overdose. After an acute of overdose, the patient should be attempted emesis or gastric lavage to decrease absorption and hemodialysis should be considered to enhance elimination. Monitor vital signs and clinical status and give supportive care.

15. **Storage Condition:** Keep in tight containers, Store below 30°C
16. **Dosage Forms and Packing Available:**
    - Letta 500 : PVC / ALU blister pack of 10 tablets in a paper box containing 1, 2, 3, 4, 6, 10, 12, 20, 25 and 50 blister(s)
    - Letta 250 : PVC / ALU blister pack of 10 tablets in a paper box containing 1, 2, 3, 4, 10, 12, 20, 25 and 50 blister(s)
17. **Name and Address of Manufacturing / Marketing Authorization Holder:**

    **MacroPhar Co., Ltd.**

    89 Soi Pattanakarn 20 Yaek 4, Pattanakarn Road, Suan Luang, Bangkok 10250
18. **Date of revision of package insert:** December 20, 2024