# Levetiracetam

# Leveget™

**250mg, 500mg, 750mg & 1g Film-Coated Tablet**

Antiepileptic

℞

**PRODUCT DESCRIPTION**
Levetiracetam (Leveget) 250mg Tablet is available as light orange colored, oblong shaped, biconvex film coated tablet, plain on both sides.
Levetiracetam (Leveget) 500mg Tablet is available as light orange colored, oblong shaped, biconvex film coated tablet plain on both sides.
Levetiracetam (Leveget) 750mg Tablet is available as light orange colored, oblong shaped, biconvex film coated tablet, plain on both sides.
Levetiracetam (Leveget) 1g Tablet is available as light orange colored, oblong shaped, biconvex film coated tablet break line on one side and plain on other side.

**FORMULATION**
Levetiracetam (Leveget) is available for oral administration as:

1) Levetiracetam (Leveget) 250mg Tablet
   Each film-coated tablet contains:
   Levetiracetam, USP...250mg

2) Levetiracetam (Leveget) 500mg Tablet
   Each film-coated tablet contains:
   Levetiracetam, USP...500mg

3) Levetiracetam (Leveget) 750mg Tablet
   Each film-coated tablet contains:
   Levetiracetam, USP...750mg

4) Levetiracetam (Leveget) 1g Tablet
   Each film-coated tablet contains:
   Levetiracetam, USP...1g

**CLINICAL PHARMACOLOGY**
**Pharmacodynamics**
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.
The mechanism of action of levetiracetam still remains to be fully elucidated. 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 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 medicinal product.

**Pharmacodynamic effects**
Levetiracetam induces seizure protection in a broad range of animal models of partial and primary generalised seizures without having a pro-convulsant effect. The primary metabolite is inactive.
In man, an activity in both partial and generalised epilepsy conditions (epileptiform discharge/ photoparoxysmal response) has confirmed the broad spectrum pharmacological profile of levetiracetam.

**Pharmacokinetics**
Levetiracetam is a highly soluble and permeable compound. The pharmacokinetic profile is linear with low intra- and intersubject variability. There is no modification of the clearance after repeated administration. There is no evidence for any relevant gender, race or circadian variability. Due to its complete and linear absorption, plasma levels can be predicted from the oral dose of levetiracetam expressed as mg/kg bodyweight. Therefore there is no need for plasma level monitoring of levetiracetam.

***Adults and adolescents***
Absorption
Levetiracetam is rapidly absorbed after oral administration. Oral absolute bioavailability is close to 100%. Peak plasma concentrations ($C_{max}$) are achieved at 1.3 hours after dosing. Steady-state is achieved after two days of a twice daily administration schedule. Peak concentrations ($C_{max}$) are typically 31 and 43 µg/ml following a single 1g dose and repeated 1g twice daily dose, respectively. The pharmacokinetics of levetiracetam are linear over the dose range of 500mg - 5 g.

*Effect of Food*
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. The extent of absorption is dose-independent and is not altered by food.

Distribution
No tissue distribution data are available in humans. Neither levetiracetam nor its primary metabolite are significantly bound to plasma proteins (< 10%). The volume of distribution of levetiracetam is approximately 0.5 to 0.7 l/kg, a value close to the total body water volume.

Metabolism
Levetiracetam is not extensively metabolised in humans. The major metabolic pathway (24% of the dose) is an 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 measurable 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.
In vitro levetiracetam and its primary metabolite have been shown not to inhibit the major human liver cytochrome P450 isoforms (CYP3A4, 2A6, 2C9, 2C19, 2D6, 2E1 and 1A2), glucuronyl transferase (UGT1A1 AND UGT1A6) and epoxide hydroxylase activities. In addition, levetiracetam does not affect the in vitro glucuronidation of valproic acid.
In human hepatocyles in culture, levetiracetam had little or no effect on CYP1A2, SULT1E1 or 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 substances, or vice versa, is unlikely.

Elimination
The plasma half-life in adults is 7±1 hours and did not vary either with dose, route of administration or repeated administration. The mean total body clearance was 0.96 ml/min/kg. The major route of excretion was via urine, accounting for a mean 95% of the dose (approximately 93% of the dose was excreted within 48 hours). Excretion via faeces accounted for only 0.3% of the dose. 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. Levetiracetam clearance is reduced in patients with renal impairment.

***Special Population***
***Elderly***
In the elderly, the half-life is increased by about 40% (10 to 11 hours). This is related to the decrease in renal function in this population.

***Renal impairment***
The apparent body clearance of both levetiracetam and of its primary metabolite is correlated to the creatinine clearance. It is therefore recommended to adjust the maintenance daily dose of levetiracetam, based on creatinine clearance in patients with moderate and severe renal impairment. In anuric end-stage renal disease adult subjects the half-life was approximately 25 and 3.1 hours during interdialytic and intradialytic periods, respectively. The fractional removal of levetiracetam was 51% during a typical 4-hour dialysis session.

***Hepatic impairment***
In subjects with mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment, the pharmacokinetics of levetiracetam were unchanged. In patients with severe hepatic impairment (Child-Pugh C), total body clearance was 50% that of normal subjects, but decreased renal clearance accounted for most of the decrease. No dose adjustment is needed for patients with hepatic impairment.

***Pediatric population***
*Children (6 to 12 years)*
Following single oral dose administration (20mg/kg) to epileptic children (6 to 12 years), 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 to 60mg/kg/day) to epileptic children (4 to 12 years), levetiracetam was rapidly absorbed. Peak plasma concentration was observed 0,5 to 1,0 hour after dosing. Linear and dose proportional increases were observed for peak plasma concentration and area under the curve. The elimination half-life was approximately 5 hours. The apparent body clearance was 1.1mL/min/kg.

*Gender*
Levetiracetam $C_{max}$ and AUC were 20% higher in women (N=11) compared to men (N=12). However, clearances adjusted for body weight were comparable.

**THERAPEUTIC INDICATIONS**
Levetiracetam (Leveget) Tablet 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.

*Adjunctive Therapy:*
- In the treatment of partial onset seizures with or without secondary generalization in adults, adolescents and children 6 years of age or above 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.

**DOSAGE & ADMINISTRATION**
Levetiracetam (Leveget) is given with or without food. The dosage regimens depends on the indication, age group, dosage form & renal function. The tablets should be swallowed whole and not be chewed or crushed.

*Monotherapy for adults and adolescents from 16 years of age*
The recommended starting dose is 250mg twice daily which should be increased to an initial therapeutic dose of 500mg twice daily after two weeks. The dose can be further increased by 250mg twice daily every two weeks depending upon the clinical response. The maximum dose is 1500mg 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 tolerability, the doily dose can be increased up to 1500 mg twice daily. Dose changes can be made in 500 mg twice daily increases or decreases every two to four weeks.

*Dosing for Partial Onset Seizures*
*Adults 16 Years and Older*
Initiate treatment with a daily dose of 1g/day, given as twice-daily dosing (500mg twice daily). Additional dosing increments may be given (1g/day additional every 2 weeks) to a maximum recommended daily dose of 3 g. There is no evidence that doses greater than 3 g/day confer additional benefit.

*Pediatric Patients (6 Years to < 16 Years)*
Initiate treatment with a daily dose of 20mg/kg in 2 divided doses (10mg/kg twice daily). Increase the daily dose every 2 weeks by increments of 20mg/kg to the recommended daily dose of 60mg/kg (30mg/kg twice daily). If a patient cannot tolerate a daily dose of 60mg/kg, the daily dose may be reduced. In the clinical trial, the mean daily dose was 44mg/kg. The maximum daily dose was 3 g/day.

For Levetiracetam (Leveget) Tablet, dosing in pediatric patients weighing 20kg to 40kg, initiate treatment with a daily dose of 500mg given as twice daily dosing (250mg twice daily). Increase the daily dose every 2 weeks by increments of 500mg to a maximum recommended daily dose of 1500mg (750mg twice daily).

For Levetiracetam (Leveget) Tablet, dosing in pediatric patients weighing more than 40kg, initiate treatment with a daily dose of 1g/day given as twice daily dosing (500mg twice daily). Increase the daily dose every 2 weeks by increments of 1g/day to a maximum recommended daily dose of 3 g (1500mg twice daily).

*Dosing for Myoclonic Seizures in Patients 12 Years of Age and Older with Juvenile Myoclonic Epilepsy*
Initiate treatment with a dose of 1g/day, given as twice-daily dosing (500mg twice daily). Increase the dosage by 1g/day every 2 weeks to the recommended daily dose of 3 g. The effectiveness of doses lower than 3 g/day has not been studied.

*Dosing for Primary Generalized Tonic-Clonic Seizures*
*Adults 16 Years and Older*
Initiate treatment with a dose of 1g/day, given as twice-daily dosing (500mg twice daily). Increase dosage by 1g/day every 2 weeks to the recommended daily dose of 3 g. The effectiveness of doses lower than 3 g/day has not been adequately studied.

*Pediatric Patients (Ages 6 to <16 Years)*
Initiate treatment with a daily dose of 20mg/kg in 2 divided doses (10mg/kg twice daily). Increase the daily dose every 2 weeks by increments of 20mg/kg to the recommended daily dose of 60mg/kg (30mg/kg twice daily). The effectiveness of doses lower than 60mg/kg/day has not been adequately studied.

*Discontinuation*
If Levetiracetam (Leveget) has to be discontinued it is recommended to withdraw it gradually (e.g. in adults and adolescents weighing more than 50kg: 500mg decreases twice daily every two to four weeks; in children and adolescents weighting less than 50kg: dose decrease should not exceed 10mg/kg twice daily every two weeks).

**Special populations**
*Elderly (65 years and older)*
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.

Dosing adjustment for adult and adolescents patients with impaired renal function.

| Group | Creatinine Clearance (ml/min/1.73m²) | Dosage and frequency |
|---|---|---|
| Normal | > 80 | 500mg to 1500mg twice daily |
| Mild | 50-79 | 500mg to 1g twice daily |
| Moderate | 30-49 | 250mg to 750mg twice daily |
| Severe | < 30 | 250mg to 500mg twice daily |
| End-stage renal disease patients undergoing dialysis[1] | - | 500mg to 1g once daily[2] |

[1] A 750mg loading dose is recommended on the first day of treatment with levetiracetam.
[2] Following dialysis, a 250mg to 500mg supplemental dose is recommended.

215mm

150mm

For children with renal impairment, levetiracetam dose needs to be adjusted based on the renal function as levetiracetam clearance is related to renal function.
Dosing adjustment for children and adolescents patients weighing less than 50kg with impaired renal function.

| Group | Creatinine Clearance (ml/min/1.73m$^2$) | Dosage and frequency |
|---|---|---|
| | | Children and adolescents weighing less than 50kg |
| Normal | > 80 | 10 to 30mg/kg twice daily |
| Mild | 50-79 | 10 to 20mg/kg twice daily |
| Moderate | 30-49 | 5 to 15mg/kg twice daily |
| Severe | < 30 | 5 to 10mg/kg twice daily |
| End-stage renal disease patients undergoing dialysis[1] | - | 10 to 20mg/kg once daily [2] |

[1] Following dialysis, a 3.5 to 7mg/kg supplemental dose is recommended.
[2] Following dialysis, a 5 to 10mg/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 < 60mL/min/1.73m$^2$.

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

*Add-on therapy for children (6 to 11 years) and adolescents (12 to 17 years) weighing less than 50kg*
The lowest effective dose should be used. The starting dose for a child or adolescent of 25kg should be 250mg twice daily with a maximum dose of 750mg twice daily.
Dose in children 50kg or greater is the same as in adults or as prescribed by physician.

**ADVERSE REACTIONS**
**Infections and infestations**
*Very Common:* nasopharyngitis
*Rare:* infection
**Blood and lymphatic system disorders**
*Uncommon:* thrombocytopenia, leukopenia
*Rare:* pancytopenia, neutropenia, agranulocytosis
**Immune system disorders**
*Rare:* drug reaction with eosinophilia and systemic symptoms (DRESS), hypersensitivity (including angioedema and anaphylaxis)
**Metabolism and nutrition disorders**
*Common:* anorexia
*Uncommon:* weight decreased, weight increase
*Rare:* hyponatraemia
**Psychiatric disorders**
*Common:* depression, hostility/aggression, anxiety, insomnia, nervousness/irritability
*Uncommon:* suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusional state, panic attack, affect lability/mood swings, agitation
*Rare:* completed suicide, personality disorder, thinking abnormal
**Nervous system disorders**
*Very common:* somnolence, headache
*Common:* convulsion, balance disorder, dizziness, lethargy, tremor
*Uncommon:* amnesia, memory impairment, coordination abnormal/ataxia, paraesthesia, disturbance in attention
*Rare:* choreoathetosis, dyskinesia, hyperkinesia
**Eye disorders**
*Uncommon:* diplopia, vision blurred
**Ear and labyrinth disorders**
*Common:* vertigo
**Respiratory, thoracic and mediastinal disorders**
*Common:* cough
**Gastrointestinal disorders**
*Common:* abdominal pain, diarrhoea, dyspepsia, vomiting, nausea
*Rare:* pancreatitis
**Hepatobiliary disorders**
*Uncommon:* liver function test abnormal
*Rare:* hepatic failure, hepatitis
**Skin and subcutaneous tissue disorders**
*Common:* rash
*Uncommon:* alopecia, eczema, pruritus
*Rare:* toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme
**Musculoskeletal and connective tissue disorders**
*Uncommon:* muscular weakness, myalgia
*Rare:* Rhabdomyolysis and blood creatine phosphokinase increased
**General disorders and administration site conditions**
*Common:* asthenia/fatigue
**Injury, poisoning and procedural complications**
*Uncommon:* injury

**CONTRAINDICATIONS**
Levetiracetam is containdiacted in patients who are hypersensitive to the active substance or other pyrrolidone derivatives or to any excipient of the product.

**PRECAUTIONS**
*Renal or hepatic impairment*
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.

*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, pyrexia, recurrent infections or coagulation disorders.

*Depression and/or suicidal ideation*
Antiepileptic drugs (AEDs), including levetiracetam, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

*Anaphylaxis and Angioedema*
Levetiracetam can cause anaphylaxis or angioedema after the first dose or at any time during treatment. If a patient develops signs or symptoms of anaphylaxis or angioedema, levetiracetam should be discontinued and the patient should seek immediate medical attention. Levetiracetam should be discontinued permanently if a clear alternative etiology for the reaction cannot be established.

*Serious Dermatological Reactions*
Serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in both pediatric and adult patients 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. Levetiracetam should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered.

*Withdrawal Seizures*
Antiepileptic drugs, including levetiracetam, should be withdrawn gradually to minimize the potential of increased seizure frequency.

*Somnolence and Fatigue*
Levetiracetam may cause somnolence, fatigue, coordination difficulties. Patients should be monitored for these signs and symptoms and advised not to drive or operate machinery until they have gained sufficient experience on levetiracetam to gauge whether it adversely affects their ability to drive or operate machinery.

*Seizure Control During Pregnancy*
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. Close monitoring should continue through the postpartum period especially if the dose was changed during pregnancy.

**Pregnancy**
Levetiracetam is not recommended during pregnancy and in women of childbearing potential not using contraception unless clearly necessary.

**Nursing Mothers**
Levetiracetam is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from levetiracetam, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

**DRUG INTERACTIONS**
*Probenecid*
Renal clearance of ucb L057 in the presence of probenecid (500 mg four times daily) decreased 60%, probably related to competitive inhibition of tubular secretion of ucb.

*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.

*Laxatives*
There have been isolated reports of decreased levetiracetam efficacy when the osmotic laxative macrogol has been concomitantly administered with oral levetiracetam. Therefore, macrogol should not be taken orally for one hour before and for one hour after taking levetiracetam.

**OVERDOSE AND TREATMENT**
The highest known dose of levetiracetam received in the clinical development program was 6 g/day. Other than drowsiness, there were no adverse reactions in the few known cases of overdose in clinical trials. Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with levetiracetam overdoses in post-marketing use.

After an acute overdose, the stomach may be emptied by induction of emesis or gastic lavage; usual precautions should be observed to maintain airway. There is no specific antidote for levetiracetam. Treatment of an overdose will be symptomatic and may include haemodialysis. 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.

**AVAILABILITY**
Levetiracetam (Leveget) 250mg Tablet are available in Alu/PVC blister pack x 10 (Box of 10 's) .
Levetiracetam (Leveget) 500mg Tablet are available in Alu/PVC blister pack x 10 (Box of 10 's).
Levetiracetam (Leveget) 750mg Tablet are available in Alu/PVC blister pack x 10 (Box of 10 's).
Levetiracetam (Leveget) 1g Tablet are available in Alu/PVC blister pack x 10 (Box of 10 's).

**STORAGE CONDITION**
Store at temperatures not exceeding 30°C.
The expiration date refers to the product correctly stored at the required conditions.

***Keep out of reach of children.***

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

For suspected adverse drug reaction, report to FDA: www.fda.gov.ph
The patient is advised to seek immediate medical attention at the first sign of adverse drug reaction.

**REGISTRATION NUMBER:**
Levetiracetam (Leveget) 250mg Tablet: DR-XY47432
Levetiracetam (Leveget) 500mg Tablet: DR-XY47433
Levetiracetam (Leveget) 750mg Tablet: DR-XY47689
Levetiracetam (Leveget) 1g Tablet: DR-XY47434

**DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION**
Levetiracetam (Leveget) 250mg Tablet:
*Initial:* 29 September 2021
Levetiracetam (Leveget) 500mg Tablet:
*Initial:* 29 September 2021
Levetiracetam (Leveget) 750mg Tablet:
*Initial:* 26 January 2022
Levetiracetam (Leveget) 1g Tablet:
*Initial:* 29 September 2021

**DATE OF REVISION:** 28-February-2022

**Please read the contents carefully before use.**
**This package insert is continually updated from time to time.**

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