Levetiracetam

Leveget™

℞

100mg/ mL (500mg/ 5mL) Solution for Injection
Antiepileptic

PRODUCT DESCRIPTION
Levetiracetam (Leveget) 100mg/ mL (500mg/ 5mL) Solution for Injection is available as clear colorless transparent liquid filled in clear glass USP Type I ampoule.

FORMULATION

Each mL contains:
Levetiracetam, USP…100mg

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 Ca2+ levels by partial inhibition of N- type Ca2+ currents and by reducing the release of Ca2+ 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
The pharmacokinetic profile has been characterized following oral administration. A single dose of 1500mg levetiracetam diluted in 100mL of a compatible diluent and infused intravenously over 15 minutes is bioequivalent to 1500mg levetiracetam oral intake, given as three 500mg tablets.
The intravenous administration of doses up to 4000mg diluted in 100mL of 0.9% sodium chloride infused over 15 minutes and doses up to 2500mg diluted in 100mL of 0.9% sodium chloride infused over 5 minutes was evaluated. The pharmacokinetic and safety profiles did not identify any safety concerns.
Levetiracetam is a highly soluble and permeable compound. The pharmacokinetic profile is linear with low intra- and inter-subject variability. There is no modification of the clearance after repeated administration. There is no evidence for any relevant gender, race or circadian variability. The pharmacokinetic profile is comparable in healthy volunteers and in patients with epilepsy.

Distribution
Peak plasma concentration (C_{max}) observed in 17 subjects following a single intravenous dose of 1500mg infused over 15 minutes was 51±19 µg/mL. 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 interdialylic 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.

Gender
Levetiracetam C_{max} and AUC were 20% higher in women compared to men. However, clearances adjusted for body weight were comparable.

THERAPEUTIC INDICATIONS
Partial Onset Seizures
Levetiracetam (Leveget) IV Injection is indicated as adjunctive therapy in the treatment of partial onset seizures in adults and children 1 month of age and older with epilepsy. Levetiracetam (Leveget) IV Injection is for intravenous use only as an alternative for patients when oral administration is temporarily not feasible.

Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy
Levetiracetam (Leveget) IV Injection is indicated as adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents 12 years of age and older with juvenile myoclonic epilepsy. Levetiracetam (Leveget) IV Injection is for intravenous use only as an alternative for patients when oral administration is temporarily not feasible.

Primary Generalized Tonic-Clonic Seizures
Levetiracetam (Leveget) IV Injection is indicated as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and children 6 years of age and older with idiopathic generalized epilepsy. Levetiracetam (Leveget) IV Injection is for intravenous use only as an alternative for patients when oral administration is temporarily not feasible.

DOSAGE & ADMINISTRATION
Dosing for Partial Onset Seizures
Adults 16 Years and Older
Initiate treatment with a daily dose of 1000mg/day, given as twice-daily dosing (500mg twice daily). Additional dosing increments may be given (1000mg/day additional every 2 weeks) to a maximum recommended daily dose of 3000mg. There is no evidence that doses greater than 3000mg/day confer additional benefit.

Pediatric Patients
1 Month to < 6 Months
Initiate treatment with a daily dose of 14mg/kg in 2 divided doses (7mg/kg twice daily). Increase the daily dose every 2 weeks by increments of 14mg/kg to the recommended daily dose of 42mg/kg (21mg/kg twice daily). In the clinical trial, the mean daily dose was 35mg/kg in this age group.

6 Months to < 4 Years
Initiate treatment with a daily dose of 20mg/kg in 2 divided doses (10mg/kg twice daily). Increase the daily dose in 2 weeks by an increment of 20mg/kg to the recommended daily dose of 50mg/kg (25mg/kg twice daily). If a patient cannot tolerate a daily dose of 50mg/kg, the daily dose may be reduced. In the clinical trial, the mean daily dose was 47mg/kg in this age group.

4 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 3000mg/day.

Dosing for Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy
Initiate treatment with a dose of 1000mg/day, given as twice-daily dosing (500mg twice daily). Increase the dosage by 1000mg/day every 2 weeks to the recommended daily dose of 3000mg.

Dosing for Primary Generalized Tonic-Clonic Seizures
Adults 16 Years and Older
Initiate treatment with a dose of 1000mg/day, given as twice-daily dosing (500mg twice daily). Increase dosage by 1000mg/day every 2 weeks to the recommended daily dose of 3000mg.

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 (10mg/kg twice daily) to the recommended daily dose of 60mg/kg (30mg/kg twice daily).

Switching from Oral Dosing
When switching from oral levetiracetam, the initial total daily intravenous dosage of levetiracetam should be equivalent to the total daily dosage and frequency of oral levetiracetam.

Switching to Oral Dosing
At the end of the intravenous treatment period, the patient may be switched to levetiracetam oral administration at the equivalent daily dosage and frequency of the intravenous administration.

Preparation and Administration Instructions
Levetiracetam (Leveget) IV Injection is for intravenous use only and should be diluted in 100mL of a compatible diluent prior to administration. If a smaller volume is required (e.g. pediatric patients), the amount of diluent should be calculated to not exceed a maximum levetiracetam concentration of 15mg per mL of diluted solution. Consideration should also be given to the total daily fluid intake of the patient. Levetiracetam (Leveget) IV Injection should be administered as a 15-minute IV infusion.

Levetiracetam (Leveget) IV Injection may be mixed with the following diluents and antiepileptic drugs. The diluted solution should not be stored for more than 4 hours at controlled room temperature [15°C-30°C].

Diluents: Sodium chloride (0.9%) Solution for Injection, Lactated Ringer's Solution for Injection, Dextrose 5% Solution for Injection.

Other Antiepileptic Drugs: Lorazepam, Diazepam, Valproate sodium

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Product with particulate matter or discoloration should not be used. Any unused portion of the Levetiracetam (Leveget) IV Injection contents should be discarded.

Adults
See Table 1 for the recommended preparation and administration of Levetiracetam (Leveget) IV Injection for adults to achieve a dose of 500mg, 1000mg, or 1500mg.

Table 1: Preparation and Administration of Levetiracetam (Leveget) 100mg/ mL (500mg/ 5mL) Solution for Injection

Dose	Withdraw Volume	Volume of Diluent	Infusion Time
500mg	5mL (5mL ampoule)	100mL	15 minutes
1000mg	10mL (two 5mL ampoules)	100mL	15 minutes
1500mg	15mL (three 5mL ampoules)	100mL	15 minutes

215mm

150mm

For example, to prepare a 1000mg dose, dilute 10mL of Levetiracetam (Leveget) IV Injection in 100mL of a compatible diluent and administer intravenously as a 15-minute infusion.

Pediatric Patients
When using Levetiracetam (Leveget) IV Injection for pediatric patients, dosing is weight-based (mg per kg).

The following calculation should be used to determine the appropriate daily dose of Levetiracetam injection for pediatric patients:

$$\text{Total daily dose (mL/day)} = \frac{\text{Daily dose (mg/kg/day) x patient weight (kg)}}{\text{100mg/ mL}}$$

Dosage Adjustments in Adult Patients with Renal Impairment
Levetiracetam dosing must be individualized according to the patient's renal function status. Recommended dosage adjustments for adults with renal impairment are shown in Table 2. Information is unavailable for dosage adjustments in pediatric patients with renal impairment. In order to calculate the dose recommended for adult patients with renal impairment, creatinine clearance adjusted for body surface area must be calculated. To do this an estimate of the patient's creatinine clearance (CLcr) in mL/min must first be calculated using the following formula:

$$CL_{cr} = \frac{[140\text{-age (years)}] \text{ x weight (kg) (x 0.85 for female patients)}}{72 \text{ x serum creatinine (mg/dL)}}$$

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

$$CL_{cr}\ (\text{mL/min/1.73m}^2) = \frac{CL_{cr}\ (\text{mL/min}) \text{ x } 1.73}{\text{BSA subject (m}^2\text{)}}$$

Table 2: Dosage Adjustment Regimen for Adult Patients with Renal Impairment.

Group	Creatinine Clearance (mL/min/1.73m^2)	Dosage (mg)	Frequency
Normal	> 80	500 to 1,500	Every 12 hours
Mild	50 – 80	500 to 1,000	Every 12 hours
Moderate	30 – 50	250 to 750	Every 12 hours
Severe	< 30	250 to 500	Every 12 hours
ESRD patients using dialysis	------	500 to 1,000[1]	Every 24 hours[1]

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

Method of Administration
Levetiracetam (Leveget) IV Injection is for intravenous use only and the recommended dose must be diluted in at least 100mL of a compatible diluent and administered intravenously as a 15-minute intravenous infusion.

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 of the excipient of 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.

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.

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.

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.

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 affect their ability to drive or operate machinery.

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

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.

Excipients
This medicinal product contains 2.5 mmol (or 57mg) sodium per maximum single dose (0.8 mmol (or 19mg) per ampoule). To be taken into consideration by patients on a controlled sodium diet.

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.

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) 100mg/ mL (500mg/ 5mL) Solution for Injection is available as 5 mL USP type I clear glass ampoule, box of 1's.

STORAGE CONDITIONS
Store at temperatures not exceeding 30°C.
Protect from sunlight.
Diluted solution must be used within 4 hours and stored in a controlled room temperature (15°C – 30°C). discard if unused.
Keep out of reach of children.

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

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

REGISTRATION NUMBER: DR-XY47793

DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION:
Initial: March 10, 2022

DATE OF REVISION OF PACKAGING INSERT: 25 April, 2022

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

Getz pharma (PVT) LIMITED
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PHP-200015476

Manufactured by: Getz Pharma (Pvt.) Ltd.,
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Imported by: Getz Pharma (Phils.) Inc.,
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