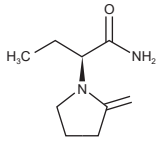
Xeticam™
[Levetiracetam]

زیٹی کیم

IV Injection 500mg/5ml

DESCRIPTION
Xeticam IV (Levetiracetam) Injection is an antiepileptic drug available for intravenous administration. The chemical name of levetiracetam, a single enantiomer, is (−)-(*S*)-α-ethyl-2-oxo-1-pyrrolidineacetamide. Its molecular formula is $C_8H_{14}N_2O_2$ and the structural formula is:



Levetiracetam

QUALITATIVE AND QUANTITATIVE COMPOSITION
Xeticam IV (Levetiracetam) Injection is available for intravenous administration as:

Xeticam IV Injection 500mg/5ml
Each 5mL ampoule contains:
Levetiracetam USP…500mg

CLINICAL PHARMACOLOGY
Mechanism of Action
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.

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 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. The major metabolite is inactive in animal seizure models. Two minor metabolites were identified as the product of hydroxylation of the 2-oxo-pyrrolidine ring (2% of dose) and opening of the 2-oxo-pyrrolidine ring in position 5 (1% of dose). There is no enantiomeric interconversion of levetiracetam or its major metabolite.

Elimination
Levetiracetam plasma half-life in adults is 7±1 hour and is unaffected by either dose or repeated administration. Levetiracetam is eliminated from the systemic circulation by renal excretion as unchanged drug which represents 66% of administered dose. The total body clearance is 0.96mL/min/kg and the renal clearance is 0.6mL/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 4mL/min/kg. 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 disposition of levetiracetam was studied in adult subjects with varying degrees of renal function. Total body clearance of levetiracetam is reduced in patients with impaired renal function by 40% in the mild group (CL_{cr} = 50-80mL/min), 50% in the moderate group (CL_{cr} = 30-50mL/min) and 60% in the severe renal impairment group (CL_{cr} <30mL/min). Clearance of levetiracetam is correlated with creatinine clearance. In anuric (end stage renal disease) patients, the total body clearance decreased 70% compared to normal subjects (CL_{cr} >80mL/min). Approximately 50% of the pool of levetiracetam in the body is removed during a standard 4 hour hemodialysis procedure.

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
Xeticam IV (Levetiracetam) 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. Xeticam IV (Levetiracetam) 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
Xeticam IV (Levetiracetam) 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. Xeticam IV (Levetiracetam) Injection is for intravenous use only as an alternative for patients when oral administration is temporarily not feasible.

Primary Generalized Tonic-Clonic Seizures
Xeticam IV (Levetiracetam) 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. Xeticam IV (Levetiracetam) 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
Xeticam IV (Levetiracetam) 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. Xeticam IV (Levetiracetam) Injection should be administered as a 15-minute IV infusion. Xeticam IV (Levetiracetam) 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 Xeticam IV (Levetiracetam) Injection contents should be discarded.

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

Table 1: Preparation and Administration of Xeticam IV (Levetiracetam) Injection for

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

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

Pediatric Patients
When using Xeticam IV (Levetiracetam) 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:

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

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:

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

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

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

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

Group	Creatinine Clearance (mL/min/1.73m²)	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
Xeticam IV (Levetiracetam) 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
Very common: Nasopharyngitis, somnolence and headache.

Common: Anorexia, depression, hostility/aggression, anxiety, insomnia, nervousness/irritability, convulsion, balance disorder, dizziness, lethargy, tremor, vertigo cough, abdominal pain, diarrhoea, dyspepsia, vomiting, nausea, rash and asthenia/fatigue.

Uncommon: Thrombocytopenia, leucopenia, weight decrease, weight increase, suicide attempt and suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusional state, panic attack, emotional instability/mood swings, agitation, amnesia, memory impairment, abnormal coordination/ataxia, paraesthesia, disturbance in attention, diplopia, vision blurred, liver function test abnormal, alopecia, eczema, pruritus, muscle weakness, myalgia and injury.

Rare: Infection, pancytopenia, neutropenia, agranulocytosis, drug reaction with eosinophilia and systemic symptoms (DRESS), hypersensitivity (including angioedema and anaphylaxis, hyponatraemia, completed suicide, personality disorder, thinking abnormal, choreoathetosis, dyskinesia, hyperkinesia, pancreatitis, hepatic failure, hepatitis, acute kidney injury, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, rhabdomyolysis and blood creatine phosphokinase increased.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

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
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.

Suicide
Anti-epileptic drugs (AEDs) including levetiracetam increase the risk of suicidal thoughts or behaviour 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
There are no adequate and controlled studies in pregnant women. Levetiracetam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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
Probenecid (500mg four times daily) has been shown to inhibit the renal clearance of the primary metabolite, but not of levetiracetam. Nevertheless, the concentration of this metabolite remains low.

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.

OVERDOSAGE
Symptoms
Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with levetiracetam overdoses.

Management of Overdose
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.

STORAGE
Do not store above 30°C.
Protect from sunlight.

The diluted solution should not be stored for more than 4 hours at controlled room temperature (15°C – 30°C).

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Xeticam IV (Levetiracetam) Injection 500mg/5mL is available in pack of 1's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

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

Manufactured by:
Getz pharma (PVT) LIMITED
www.getzpharma.com
29-30/27, K.I.A., Karachi, Pakistan
L-200011577