Xeticam™

[L e v e t i r a c e t a m]

Oral Solution 100mg/mL

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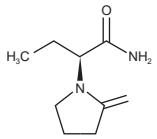
DESCRIPTION

XETICAM (Levetiracetam) Oral Solution is an antiepileptic drug available for oral 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 (Levetiracetam) Oral Solution is available for administration as:

XETICAM Oral Solution 100mg/mL
Each ml contains:
Levetiracetam USP… 100mg

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

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 1000mg dose and repeated 1000mg twice daily dose, respectively. The pharmacokinetics of levetiracetam are linear over the dose range of 500mg - 5000mg.

Effect of Food

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). No enantiomeric interconversion was evidenced in-vivo for either levetiracetam or its primary metabolite.

Elimination

The plasma half-life in adults was 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 in-vivo feces 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.

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} = 50-80 mL/min), 50% in the moderate group (CL_{cr} = 30-50 mL/min) and 60% in the severe renal impairment group (CL_{cr} <30 mL/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} > 80 mL/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.

Pediatric population

Children (6 to 12 years)

Following single oral dose administration (20 mg/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 60 mg/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.

Infants and children (1 month to 4 years)

Following single dose administration (20mg/kg) of a 100mg/ml oral solution to epileptic children (1 month to 4 years), levetiracetam was rapidly absorbed and peak plasma concentrations were observed approximately 1 hour after dosing. The pharmacokinetic results indicated that half-life was shorter (5.3 h) than for adults (7.2h) and apparent clearance was faster (1.5 ml/min/kg) than for adults (0.96 ml/min/kg).

Gender

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

THERAPEUTIC INDICATIONS

XETICAM (Levetiracetam) is indicated as:

Monotherapy:

- in the treatment of partial onset seizures with or without secondary generalisation 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 generalisation in adults, adolescents, children and infants from 1 month of age 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 generalised tonic-clonic seizures in adults and adolescents from 6 years of age with Idiopathic Generalised Epilepsy.

DOSAGE & ADMINISTRATION

XETICAM (Levetiracetam) Oral Solution may be diluted in a glass of water or baby's bottle and may be taken with or without food. The dosage regimens depends on the indication, age group, dosage form & renal function. Prescribe the oral solution for pediatric patients with body weight ≤20 kg. Prescribe the oral solution or tablets for pediatric patients with body weight above 20 kg.

When using the oral solution in pediatric patients, dosing is weight-based (mg per kg) using a calibrated measuring device (not a household teaspoon or tablespoon).

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.

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).

Pediatric Patients (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.

Pediatric Patients (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. The maximum daily dose was 3000mg/day.

XETICAM (Levetiracetam) Oral Solution Weight-Based Dosing Calculation For Pediatric Patients

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

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

Dosing for Myoclonic Seizures in Patients 12 Years of Age and Older 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. The effectiveness of doses lower than 3000mg/day has not been studied.

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. The effectiveness of doses lower than 3000mg/day has not been adequately studied.

Pediatric Patients (Aged 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 XETICAM (Levetiracetam) 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 infants older than 6 months, children and adolescents weighting less than 50kg: dose decrease should not exceed 10mg/kg twice daily every two weeks; in infants (less than 6 months): dose decrease should not exceed 7mg/ kg twice daily every two weeks).

Special Population

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 individualised 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 Clearence (ml/min/1.73m^2)	Dosage and frequency
Normal	> 80	500mg to 1500mg twice daily
Mild	50-79	500mg to 1000mg 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 1000mg 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.

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 Clearence (ml/min/1.73m²)	Dosage and frequency[1]	
		Infants 1 to less than 6 months	Infants 6 to 23 months, children and adolescents weighing less than 50 kg
Normal	> 80	7 to 21 mg/kg (0.07 to 0.21 ml/kg) twice daily	10 to 30 mg/kg (0.10 to 0.30 ml/kg) twice daily
Mild	50 - 79	7 to 14 mg/kg (0.07 to 0.14 ml/kg) twice daily	10 to 20 mg/kg (0.10 to 0.20 ml/kg) twice daily
Moderate	30 - 49	3.5 to 10.5 mg/kg (0.035 to 0.105 ml/kg) twice daily	5 to 15 mg/kg (0.05 to 0.15 ml/kg) twice daily
Severe	< 30	3.5 to 7 mg/kg (0.035 to 0.07 ml/kg) twice daily	5 to 10 mg/kg (0.05 to 0.10 ml/kg) twice daily
End-stage renal disease patients undergoing dialysis	-	7 to 14 mg/kg (0.07 to 0.14 ml/kg) once daily[2][4]	10 to 20 mg/kg (0.10 to 0.20 ml/kg) once daily[3][5]

[1] Levetiracetam Oral Solution should be used for doses under 250mg, for doses not multiple of 250mg when dosing recommendation is not achievable by taking multiple tablets and for patients unable to swallow tablets.
[2] A 10.5mg/kg (0.105ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.
[3] A 15mg/kg (0.15ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.
[4] Following dialysis, a 3.5 to 7mg/kg (0.035 to 0.07ml/kg) supplemental dose is recommended.
[5] Following dialysis, a 5 to 10mg/kg (0.05 to 0.10ml/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/1.73m².

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 infants aged 6 to 23 months, children (2 to 11 years) and adolescents (12 to 17 years) weighing less than 50 kg
The initial therapeutic dose is 10mg/kg twice daily. Depending upon the clinical response and tolerability, the dose can be increased up to 30mg/kg twice daily. Dose changes should not exceed increases or decreases of 10mg/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 infants from 6 months of age, children and adolescents:

Weight	Starting dose: 10mg/kg twice daily	Maximum dose: 30mg/kg twice daily
6kg[1]	60mg (0.6ml) twice daily	180mg (1.8ml) twice daily
10kg[1]	100mg (1ml) twice daily	300mg (3ml) twice daily
15kg[1]	150mg (1.5ml) twice daily	450mg (4.5ml) twice daily
20kg[1]	200mg (2ml) twice daily	600mg (6ml) twice daily
25kg	250mg twice daily	750mg twice daily
From 50kg[2]	500mg twice daily	1,500mg twice daily

[1] Children 25kg or less should preferably start the treatment with Levetiracetam Oral Solution.
[2] Dose in children and adolescents 50kg or more is the same as in adults.

Add-on therapy for infants aged from 1 month to less than 6 months
The initial therapeutic dose is 7mg/kg twice daily. Depending upon the clinical response and tolerability, the dose can be increased up to 21mg/kg twice daily. Dose changes should not exceed increases or decreases of 7mg/kg twice daily every two weeks. The lowest effective dose should be used.
Infants should start the treatment with Levetiracetam Oral Solution.

Dose recommendations for infants aged from 1 month to less than 6 months

Weight	Starting dose: 7mg/kg twice daily	Maximum dose: 21mg/kg twice daily
4kg	28mg (0.3ml) twice daily	84mg (0.85ml) twice daily
5kg	35mg (0.35ml) twice daily	105mg (1.05ml) twice daily
7kg	49mg (0.5ml) twice daily	147mg (1.5ml) twice daily

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 contraindicated in patients who are hypersensitive to the active substance or other pyrrolidone derivatives or to any of the excipient of product.

PRECAUTIONS
Renal 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.

Suicide
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
As with most antiepileptic drugs, levetiracetam should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus. If withdrawal is needed because of a serious adverse reaction, rapid discontinuation can be considered.

Somnolence and Fatigue
Levetiracetam may cause somnolence, fatigue and 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.

Behavioral Abnormalities and Psychotic Symptoms
Levetiracetam may cause behavioral abnormalities and psychotic symptoms. Patients treated with levetiracetam should be monitored for psychiatric signs and symptoms.

Increase in Blood Pressure
Monitor patients 1 month to <4 years of age for increases in diastolic blood pressure.

Worsening of seizures
As with other types of antiepileptic drugs, levetiracetam may rarely exacerbate seizure frequency or severity. This paradoxical effect was mostly reported within the first month after levetiracetam initiation or increase of the dose, and was reversible upon drug discontinuation or dose decrease. Patients should be advised to consult their physician immediately in case of aggravation of epilepsy.

Electrocardiogram QT interval prolongation
Levetiracetam should be used with caution in patients with QTc-interval prolongation, in patients concomitantly treated with drugs affecting the QTc-interval, or in patients with relevant pre-existing cardiac disease or electrolyte disturbances.

Excipients
Levetiracetam Oral Solution contains methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed). It also contains maltitol liquid; patients with rare hereditary problems of fructose intolerance should not take this medicinal product.

Pregnancy
There are no adequate and controlled studies in pregnant women. In animal studies, levetiracetam produced evidence of developmental toxicity, including teratogenic effects, at doses similar to or greater than human therapeutic doses. 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
Renal clearance of ucb L057 in the presence of probenecid 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.

OVERDOSAGE
The highest known dose of levetiracetam received in the clinical development program was 6000mg/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.

Management of overdose
There is no specific antidote for overdose with levetiracetam. If indicated, elimination of unabsorbed drug should be attempted by emesis or gastric lavage; usual precautions should be observed to maintain airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the patient's clinical status.

STORAGE
Do not store above 30°C.
Protect from light.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
XETICAM (Levetiracetam) Oral Solution 100mg/ml is available in bottle of 60ml.

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:
Herbion Pakistan (Pvt.) Ltd,
Industrial Triangle, Kahuta Road, Islamabad, Pakistan.

Manufactured for:
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