Lecetam

(Levetiracetam) USP

100mg/ml

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(لیویٹائراسٹام) یو ایس پی

COMPOSITION FOR INJECTION & ORAL SOLUTION
Each ml Contains
Levetiracetam USP.....100mg

DESCRIPTION
Levetiracetam is an antiepileptic medicine (a medicine used to treat seizures in epilepsy). Levetiracetam is chemically described as 1-Pyrrolidineacetamide, α-ethyl-2-oxo-, (αS). Its empirical formula is $C_8H_{14}N_2O_2$.

CLINICAL PHARMACOLOGY
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.

Pharmacokinetic Properties
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 43µg/ml following a single 1000mgdose and repeated 1000mg twice daily dose, respectively. 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.
Biotransformation
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. 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 hepatocytes in culture, Levetiracetam did not cause enzyme induction. Therefore, the interaction of Levetiracetam with other substances, or vice versa, is unlikely.
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 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 metabolite 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.
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.
Children (4 to 12 years)
Following single oral dose administration (20mg/kg) to epileptic children (6 to 12 years), the half-life of Levetiracetam was 6.0 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. 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) orally 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 (7.2 h) and apparent clearance was faster (1.5ml/min/kg) than for adults (0.96ml/min/kg).

INDICATIONS AND USAGE
Levetiracetam is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalistion in patients from 16 years of age with newly diagnosed epilepsy.
Levetiracetam is indicated as adjunctive therapy:

- In the treatment of partial onset seizures with or without secondary generalization in adults and children from 4 years 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-cloic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy.

DOSAGE AND ADMINISTRATION
Injection:
Lecetam Injection must be diluted prior to administration.
The daily dose of Levetiractam is administered in two equally divided doses.

- **Monotherapy**

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 50kg or more
The initial therapeutic dose is 500mg twice daily. This dose can be started on the first day of treatment. Depending upon the clinical response and tolerability, the daily dose can be increased up to 1500mg twice daily. Dose changes can be made in 500mg twice daily increases or decreases every two to four weeks.
Children aged 4 to 11 years and adolescents (12 to 17 years) weighing less than 50kg
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.

Weight	Starting dose:	Maximum dose:
8Kg	7g/Kg twice daily	14mg/Kg daily
15Kg	150mg twice daily	450mg twice daily
20Kg	200mg twice daily	600mg twice daily
25Kg	250mg twice daily	750mg twice daily
From 50Kg	500mg twice daily	1500mg twice daily

Dosage in children 50kg or greater is the same as in adults.
The physician should prescribe the most appropriate pharmaceutical form and strength according to weight and dose.
Dosage recommendations for children and adolescents:
Infants and children less than 4 years
1 Month To <6 Months
Treatment should be initiated with a daily dose of 14mg/kg in 2 divided doses (7mg/kg twice daily). The daily dose should be increased every 2 weeks by increments of 14mg/kg to the recommended daily dose of 42mg/kg (21mg/kg twice daily).
6 Months To <4 Years
Treatment should be initiated with a daily dose of 20mg/kg in 2 divided doses (10mg/kg twice daily). The daily dose should be increased 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.
Elderly (65 years and older)
Dose adjustment is recommended in elderly patients with compromised renal function (see "Patients with renal impairment" below)
Patients with 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. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in ml/min is needed. The CLcr in ml/min may be estimated from serum creatinine (mg/dl) determination using the following formula:

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

Dosing adjustment for adult patients with impaired renal function

Group	Creatinine Clearance (ml/min/1.73 m²)	Dosage and frequency)
Normal	> 80	500 to 1500 mg twice daily
Mild	50-79	500 to 1000 mg twice daily
Moderate	30-49	250 to 750 mg twice daily
Severe	<30	250 to 500 mg twice daily
End-stage renal disease patients Undergoing dialysis	-	500 to 1000 mg once daily

(1) A 750mg loading dose is recommended on the first day of treatment with Levetiracetam.
(2) Following dialysis, a 250 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.
This recommendation is based on a study in adult renally impaired patients.

The CLcr in ml/min/1.73m^2 may be estimated from serum creatinine (mg/dl) determination, for young adolescents and children using the following formula (Schwartz formula):

$$\text{CLcr (ml/min/1.73m}^2\text{)} = \frac{\text{Height (cm) x ks}}{\text{Serum Creatinine (mg/dl)}}$$

ks= 0.55 in Children to less than 13 years and in adolescent female; ks= 0.7 in adolescent male Dosing adjustment for children and adolescent patients weighing less than 50kg with impaired renal function:

Group	Creatinine Clearance (ml/min/1.73 m^2)	Dosage and frequency) Children from 4 years and adolescents weight less than 50kg
Normal	> 80	10 to 30mg/kg (0.10 to 0.30 ml/kg twice daily
Mild	50-79	10 to 20mg/kg (0.10 to 0.20 ml/kg twice daily
Moderate	30-49	5 to 15mg/kg (0.05 to 0.15 ml/kg twice daily
Severe	<30	5 to 10mg/kg (0.05 to 0.10 ml/kg twice daily
End-stage renal disease patients Undergoing dialysis	-	10 to 20mg/kg (0.10 to 0.20 ml/kg twice daily

(1) A 15mg/kg (0.15ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.
(2) Following dialysis, a 5 to 10mg/kg (0.05 to 0.10ml/kg) supplemental dose is recommended.

Patients with 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 <70ml/min.

CONTRAINDICATIONS
Hypersensitivity to Levetiracetam or other pyrrolidone derivatives or any of the excipients.

ADVERSE REACTIONS
The most common undesirable effects are somnolence, asthenia and dizziness.

General disorders and administration site conditions
Very common: asthenia
Nervous system disorders
Very common: somnolence
Common amnesia, ataxia, convulsion, dizziness, headache, tremor
Psychiatric disorders
Common: depression, emotional lability, hostility, insomnia, nervousness.
Metabolism and nutrition disorders
Common: anorexia
Ear and labyrinth disorders
Common: vertigo
Eye disorders
Common: diplopia
Injury, poisoning and procedural complications
Common accidental injury
Skin and subcutaneous tissue disorders
Common: rash, alopecia
Blood and lymphatic system disorders
Common: Thrombocytopenia

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS
If Levetiracetam has to be discontinued it is recommended to withdraw it gradually (e.g. 500mg twice daily decrements every two to four weeks). In a study reflecting clinical practice, the concomitant antiepileptic medication could be withdrawn in a limited number of patients who responded to Levetiracetam adjunctive therapy (36 patients out of 69). An increase in seizure frequency of more than 25% has been reported in 14 % and 26 % of the Levetiracetam and placebo treated patients, respectively. The administration of Levetiracetam to patients with renal impairment may require dose adaptation. In patients with severely impaired hepatic function, assessment of renal function is recommended before dose selection.

DRUG INTERACTIONS
Levetiracetam did not influence the serum concentrations of existing antiepileptic medicinal products (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these antiepileptic medicinal products did not influence the pharmacokinetics of Levetiracetam.
Probenecid (500mg four times daily), a renal tubular secretion blocking agent, has been shown to inhibit the renal clearance of the primary metabolite but not of Levetiracetam. Nevertheless, the concentration of this metabolite remains low. It is expected that other drugs excreted by active tubular secretion could also reduce the renal clearance of the metabolite. The effect of Levetiracetam on probenecid was not studied and the effect of Levetiracetam on other actively secreted drugs, e.g. NSAIDs, sulphonamides and methotrexate is unknown. Levetiracetam 1000 mg daily did not influence the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel); endocrine parameters (luteinizing hormone and progesterone) were not modified. Levetiracetam 2000 mg daily did not influence the pharmacokinetics of digoxin and warfarin; prothrombin times were not modified. Coadministration with digoxin, oral contraceptives and warfarin did not influence the pharmacokinetics of Levetiracetam.
No data on the influence of antacids on the absorption of Levetiracetam are available. The extent of absorption of Levetiracetam was not altered by food, but the rate of absorption was slightly reduced.
No data on the interaction of Levetiracetam with alcohol are available.

PREGNANCY AND LACTATION
There are no adequate data from the use of Levetiracetam in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for human is unknown. Levetiracetam should not be used during pregnancy unless clearly necessary. Discontinuation of antiepileptic treatments may result in disease worsening, harmful to the mother and the fetus.
Levetiracetam is excreted in human breast milk. Therefore, breast-feeding is not recommended.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
No studies on the effects on the ability to drive and use machines have been performed. Due to possible different individual sensitivity, some patients might experience, at the beginning of treatment or following a dose increase, somnolence or other central nervous system related symptoms. Therefore, caution is recommended in those patients when performing skilled tasks, e.g. driving vehicles or operating machinery.

OVERDOSAGE
Symptoms
Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with Levetiracetam overdoses.
Management of overdose
After an acute overdose, the stomach may be emptied by gastric lavage or by induction of emesis. 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
Store below 30°C.
Protect from heat and light.

PRESENTATION
Lecetam (Levetiracetam) Oral Solution 100mg/ml is available as pack of 60ml.
Lecetam (Levetiracetam) Injection 500mg/5ml is available as pack of one ampoule.

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

Keep all medicines out of the reach of children.

Manufactured by :
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