Levotam

(Levetiracetam)

Tablets & Oral Solution

لیووٹام

(لیویٹائراسٹام)

ٹیبلیٹس اور اورل سلوشن

DESCRIPTION

Levetiracetam is an antiepileptic drug available as Levotam tablets 250 mg and 500 mg, and Levotam Oral Solution 100 mg / ml for oral use.

COMPOSITION

Levotam Tablet 250 mg
Each film coated tablet contains:
Levetiracetam ..... 250 mg.
Product Complies U.S.P Specs

Levotam Tablet 500 mg
Each film coated tablet contains:
Levetiracetam ..... 500 mg.
Product Complies U.S.P Specs

Levotam Oral Solution 100 mg / ml
Each ml contains:
Levetiracetam ..... 100 mg.
Product Complies U.S.P Specs

INDICATIONS AND USAGE

Levetiracetam is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalization 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 1 month of age and older with epilepsy.
- In the treatment of myoclonic seizures in adults and adolescents 12 years of age and older with juvenile myoclonic epilepsy.
- In the treatment of primary generalized tonic-clonic seizures in adults and children 6 years of age and older with idiopathic generalized epilepsy.

DOSAGE AND ADMINISTRATION

Partial Onset Seizures

Adults 16 Years and Older

Treatment should be initiated with a daily dose of 1000 mg / day, given as twice-daily dosing (500 mg twice daily). Additional dosing increments may be given (1000 mg / day additional every 2 weeks) to a maximum recommended daily dose of 3000 mg.

Pediatric Patients

1 Month to < 6 Months

Treatment should be initiated with a daily dose of 14 mg / kg in 2 divided doses (7 mg / kg twice daily). The daily dose should be increased every 2 weeks by increments of 14 mg / kg to the recommended daily dose of 42 mg / kg (21 mg / kg twice daily). In the clinical trial, the mean daily dose was 35 mg / kg in this age group.

6 Months to <4 Years:

Treatment should be initiated with a daily dose of 20 mg / kg in 2 divided doses (10 mg / kg twice daily). The daily dose should be increased in 2 weeks by an increment of 20 mg / kg to the recommended daily dose of 50 mg / kg (25 mg / kg twice daily).

4 Years to < 16 Years

Treatment should be initiated with a daily dose of 20 mg / kg in 2 divided doses (10 mg / kg twice daily). The daily dose should be increased every 2 weeks by increments of 20 mg / kg to the recommended daily dose of 60 mg / kg (30 mg / kg twice daily).

For levetiracetam tablet dosing in pediatric patients weighing 20 to 40 kg, treatment should be initiated with a daily dose of 500 mg given as twice daily dosing (250 mg twice daily). The daily dose should be increased every 2 weeks by increments of 500 mg to a maximum recommended daily dose of 1500 mg (750 mg twice daily).

For levetiracetam tablet dosing in pediatric patients weighing more than 40 kg, treatment should be initiated with a daily dose of 1000 mg / day given as twice daily dosing (500 mg twice daily). The daily dose should be increased every 2 weeks by increments of 1000 mg / day to a maximum recommended daily dose of 3000 mg (1500 mg twice daily).

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:

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

Myoclonic Seizures

Patients 12 Years of Age and Older with Juvenile Myoclonic Epilepsy

Treatment should be initiated with a dose of 1000 mg / day, given as twice-daily dosing (500 mg twice daily). Dosage should be increased by 1000 mg / day every 2 weeks to the recommended daily dose of 3000 mg. The effectiveness of doses lower than 3000 mg / day has not been studied.

Primary Generalized Tonic-Clonic Seizures

Adults 16 Years and Older

Treatment should be initiated with a dose of 1000 mg / day, given as twice-daily dosing (500 mg twice daily). Dosage should be increased by 1000 mg / day every 2 weeks to the recommended daily dose of 3000 mg. The effectiveness of doses lower than 3000 mg / day has not been adequately studied.

Pediatric Patients Ages 6 to less than 16 Years

Treatment should be initiated with a daily dose of 20 mg / kg in 2 divided doses (10 mg / kg twice daily). The daily dose should be increased every 2 weeks by increments of 20 mg / kg to the recommended daily dose of 60 mg / kg (30 mg / kg twice daily). The effectiveness of doses lower than 60 mg / kg/day has not been adequately studied.

Adult Patients with Impaired Renal Function

Levetiracetam dosing must be individualized according to the patient's renal function status. Recommended doses and adjustment for dose for adults are shown in Table 1. In order to calculate the dose recommended for 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:

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

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

$$\text{CLcr (ml/min/1.73m}^2\text{)} = \frac{\text{CLcr (ml/min)}}{\text{BSA subject (m}^2\text{)}} \times 1.73$$

Dosing Adjustment Regimen For Adult Patients With Impaired Renal Function

*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*	Every 24 hours*

* Following dialysis, a 250 to 500 mg supplemental dose is recommended.

CLINICAL PHARMACOLOGY

Mechanism of Action

The precise mechanism of action is unknown. However studies indicate that the binding site is the synaptic vesicle protein SV2A, thought to be involved in the regulation of vesicle exocytosis. These findings suggest that the interaction of levetiracetam with the SV2A protein may contribute to the antiepileptic mechanism of action of the drug.

In vitro and in vivo recordings of epileptiform activity from the hippocampus have shown that levetiracetam inhibits burst firing without affecting normal neuronal excitability, suggesting that levetiracetam may selectively prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity.

Pharmacokinetics

Levetiracetam is rapidly and almost completely absorbed after oral administration. The extent of bioavailability of Levetiracetam is not affected by food.

Absorption and Distribution: Absorption of levetiracetam is rapid, with peak plasma concentrations occurring in about an hour following oral administration in fasted subjects. The oral bioavailability of levetiracetam tablets is 100% and the tablets and oral solution are bioequivalent in rate and extent of absorption. 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 pharmacokinetics of levetiracetam are linear over the dose range of 500-5000 mg. Steady state is achieved after 2 days of multiple twice-daily dosing. Levetiracetam and its major metabolite are less than 10% bound to plasma proteins; clinically significant interactions with other drugs through competition for protein binding sites are therefore unlikely.

Metabolism: Levetiracetam is not extensively metabolized in humans. The major metabolic pathway is the enzymatic hydrolysis of the acetamide group, and is reportd to be inactive.

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 0.96 ml/min/kg and the renal clearance is 0.6 ml/min/kg. The mechanism of excretion is glomerular filtration with subsequent partial tubular reabsorption. Levetiracetam elimination is correlated to creatinine clearance and is reduced in patients with impaired renal function.

Pharmacokinetic Interactions

In vitro data on metabolic interactions indicate that levetiracetam is unlikely to produce, or be subject to, pharmacokinetic interactions. Levetiracetam and its major metabolite, at concentrations well above Cmax levels achieved within the therapeutic dose range, are neither inhibitors of, nor high affinity substrates for, human liver cytochrome P_{450} isoforms, epoxide hydrolase or UDP-glucuronidation enzymes. In addition, levetiracetam does not affect the in vitro glucuronidation of valproic acid.

Special Populations

Pediatric Population: Following single oral dose administration (20 mg / 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 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 concentrations and area under the curve. The elimination half-life was approximately 5 hours. The apparent body clearance was 1.1 ml / min / kg.

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.

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 hours dialysis session.

Hepatic Impairment: In subjects with mild and moderate hepatic impairment, there was no relevant modification of the clearance of levetiracetam. In most subjects with severe hepatic impairment, the clearance of levetiracetam was reduced by more than 50% due to concomitant renal impairment.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to levetiracetam or any of the inactive ingredients.

WARNINGS

Suicidal Behavior and 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.

Neuropsychiatric Adverse Events

Adults patients - Experiencing partial onset seizures, Levetiracetam use is associated with the occurrence of central nervous system adverse events that can be classified into: a).somnolence and fatigue, b) coordination difficulties; and c) behavioral abnormalities. Somnolence, asthenia and coordination difficulties occurred most frequently within the first 4 weeks of treatment.

Pediatric Patients - Levetiracetam is associated with somnolence, fatigue, and behavioral abnormalities.

Withdrawal seizures

Antiepileptic drugs, including Levetiracetam, should be withdrawn gradually to minimize the potential of increased seizure frequency

PRECAUTIONS

Hematologic Abnormalities

In Adult Patients, minor, but statistically significant, decreases in total mean RBC count, mean hemoglobin, and mean hematocrit, were seen in Levetiracetam-treated patients in controlled trials.

In Pediatric Patients minor, but statistically significant, decreases in WBC and neutrophil counts were seen in Levetiracetam-treated patients.

Hepatic Abnormalities

No meaningful changes in liver function tests (LFT) are reported. Hence no dose adjustment is needed for patients with hepatic impairment.

Laboratory Tests

Generally most laboratory tests are not systematically altered by levetiracetam. However, there have been relatively infrequent abnormalities seen in hematologic parameters and liver function tests of patients using levetiracetam.

Drug Interactions

Levetiracetam has low potential to produce pharmacokinetic interactions. Levetiracetam and its major metabolite are neither Inhibitors nor high affinity substrates for human liver cytochrome P_{450} isoforms, or UDP-glucuronidation enzymes. Levetiracetam circulates largely unbound (<10% bound) to plasma proteins; clinically significant interactions with other drugs through competition for protein binding sites are therefore unlikely.

Effect of AEDs in pediatric patients

There was about a 22% increase of apparent total body clearance of levetiracetam when it was co-administered with enzyme-inducing AEDs. Dose adjustment is not recommended. Levetiracetam had no effect on plasma concentrations of carbamazepine, valproate, topiramate, or lamotrigine.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Carcinogenesis

No evidence of carcinogenicity has been reported with doses about 6 times higher than the maximum daily doses of levetiracetam.

Mutagenesis

Levetiracetam was not mutagenic in the Ames test or in mammalian cells In vitro in the Chinese hamster ovary/HGPAT locus assay.

Impairment of Fertility

No adverse effects on male or female fertility or reproductive performance in rats at doses up to 1800 mg / kg/day.

Pregnancy

Levetiracetam is pregnancy Category C; there are no adequate and well-controlled studies in pregnant women. Levetiracetam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of levetiracetam on labor and delivery in humans is unknown.

Lactation

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

Pediatric Use

The safety and effectiveness of levetiracetam in the adjunctive treatment of partial onset seizures in pediatric patient's age 1 month to 16 years old with epilepsy have been established. The dosing recommendation in these pediatric patients varies according to age group and is weight-based.

The safety and effectiveness of levetiracetam as adjunctive treatment of myoclonic seizures in adolescents 12 years of age and older with juvenile myoclonic epilepsy have been established.

The safety and effectiveness of levetiracetam as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in pediatric patients 6 years of age and older with idiopathic generalized epilepsy have been established.

Geriatric Use

No overall differences in safety were observed between geriatric and younger subjects. Levetiracetam is known to be substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Patients with impaired renal function

Clearance of levetiracetam is decreased in patients with renal impairment and is correlated with creatinine clearance. Caution should be taken in dosing patients with moderate and severe renal impairment and in patients undergoing hemodialysis. The dosage should be reduced in patients with impaired renal function receiving Levetiracetam and supplemental doses should be given to patients after dialysis.

ADVERSE REACTIONS

Most common adverse reactions include:

In Adult Patients: somnolence, asthenia, infection and dizziness.

In Pediatric Patients: fatigue, aggression, nasal congestion, decreased appetite, and irritability.

OVERDOSAGE

Doses as high as 6000 mg / day have been studied. In addition to drowsiness, Cases of somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma have been reported with levetiracetam overdoses.

PRESENTATION

Levotam 250 mg Tablets

Alu-Alu Blister pack of 1x10s.

Alu-Alu Blister pack of 3x10s.

Levotam 500 mg Tablets

Alu-Alu Blister pack of 1x 10s.

Levotam Oral Solution 100 mg / ml

60 ml in glass bottle with dosing dropper.

STORAGE

Store below 30°C, in a dry place, protect from light.
To be dispensed on the prescription of a registered medical practitioner only.
Keep out of the reach of children.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر خشک جگہ پر رکھیں،
روشنی سے بچائیں۔صرف رجسٹرڈ ڈاکٹر کے نسخے پر فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔

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