TORLEVA

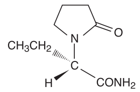
(Levetiracetam Tablets 250 mg, 500 mg, 750 mg & 1000 mg)

COMPOSITION

Each film coated tablet contains:
Levetiracetam USP 250 mg, 500 mg, 750 mg & 1000 mg

DESCRIPTION

Levetiracetam is an antiepileptic drug available as 250 mg, 500 mg, 750 mg and 1000 mg tablets for oral administration.
The chemical name of levetiracetam, is (-)-(S)- -ethyl-2-oxo-1-pyrrolidine acetamide, its molecular formula is $C_8H_{14}N_2O_2$ and its molecular weight is 170.21. Levetiracetam is chemically unrelated to existing antiepileptic drugs (AEDs).
It has the following structural formula:



Levetiracetam is a white to off-white crystalline powder with a faint odour and a bitter taste. It is highly soluble in water (104.0g/100 mL). It is also freely soluble in chloroform (65.3 g/100 mL), methanol (53.6 g/100 mL), ethanol (16.5 /100 mL) and sparingly soluble in acetonitrile (5.7 g/100 mL).

CLINICAL PHARMACOLOGY

Mechanism of Action

The precise mechanism(s) by which levetiracetam exerts its antiepileptic effect is unknown and does not appear to derive from any interaction with known mechanisms involved in inhibitory and excitatory neurotransmission. The antiepileptic activity of levetiracetam was evaluated in animal models of epileptic seizures. Levetiracetam did not inhibit single seizures induced by maximal stimulation with electrical current or different chemoconvulsants and showed only minimal activity in sub maximal stimulation and in threshold tests. Protection was observed, however, against secondarily generalized activity from focal seizures induced by pilocarpine and kainic acid, two chemoconvulsants that induce seizures that mimic some features of human complex partial seizures with secondary generalization. Levetiracetam also displayed inhibitory properties in the kindling model in rats, another model of human complex partial seizures, both during kindling development and in the fully kindled state. The predictive value of these animal models for specific types of human epilepsy is uncertain.
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

The pharmacokinetics of levetiracetam has been studied in healthy adult subjects, adults and pediatric patients with epilepsy, elderly subjects and subjects with renal and hepatic impairment.

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%. Food does not affect the extent of absorption of levetiracetam but it decreases Cmax by 20% and delays Tmax by 1.5 hours. 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.

Metabolism & Elimination

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%) and is not dependent on any liver cytochrome P450 isoenzymes. The major metabolite is inactive in animal seizure models. There is no enantiomeric interconversion of levetiracetam or its major metabolite.
Levetiracetam plasma half-life in adults is 7 ± 1 hour. 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.

Special Population

Elderly

The total body clearance is reported to decrease by 38% and the half life to be 2.5 hours longer in the elderly following oral administration of levetiracetam twice daily dosing for 10 days it is reported that compared to healthy adults.

Paediatric Patients

The apparent clearance of levetiracetam is reported to be approximately 40% higher in adults when evaluated in paediatric patients (6-12 years) after single dose (20 mg/kg).

Gender

Levetiracetam Cmax and AUC were reported to be 20% higher in women compared to men. However, clearances adjusted for body weight are comparable.

Renal Impairment

Total body clearance of levetiracetam is reduced in patients with impaired renal function by 40% in the mild group (CLcr = 50-80 mL/min), 50% in the moderate group (CLcr = 30-50 mL/min), and 60% in the severe renal impairment group (CLcr <30 mL/min). Clearance of levetiracetam is correlated with creatinine clearance. Dosage should be reduced in patients with impaired renal function receiving levetiracetam, and supplemental doses should be given to patients after dialysis.

Hepatic Impairment

In subjects with mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment, the pharmacokinetics of levetiracetam were reported to be 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.

INDICATIONS

Levetiracetam is indicated as adjunctive therapy in the treatment of partial onset seizures in adults and children 4 years of age and older with epilepsy.

CONTRAINDICATIONS

Levetiracetam is contraindicated in those hypersensitive to levetiracetam or any of its components.

WARNINGS

Neuropsychiatric Adverse Events

In adults, levetiracetam use is associated with the occurrence of central nervous system adverse events that can be classified into the following categories: 1) somnolence and fatigue, 2) coordination difficulties, and 3) behavioural abnormalities. In pediatric patients, levetiracetam is associated with somnolence, fatigue, and behavioural abnormalities.
Somnolence, asthenia and coordination difficulties occurred most frequently within the first 4 weeks of treatment.

Withdrawal Seizures

Levetiracetam should be withdrawn gradually to minimize the potential of increased seizure frequency.

PRECAUTIONS

Haematologic Abnormalities

Adults

Minor, but statistically significant decreases in total mean RBC count (0.03 x 106/mm3); mean haemoglobin (0.09 g/dL) and mean haematocrit (0.38%) were reported in levetiracetam treated patients. Significant (2.8 x 109/L) decrease in WBC and significant (1.0 x 109/L) decrease in neutrophil count were also reported in levetiracetam treated patients.

Pediatric Patients

Minor, but statistically significant decreases in WBC and neutrophil counts, increase in mean relative lymphocyte counts were reported in levetiracetam treated patients.

DRUG INTERACTIONS

Levetiracetam is unlikely to produce, or be subject to, pharmacokinetic interactions. Levetiracetam and its major metabolite, at concentrations well above Cmax level achieved within the therapeutic dose range, are neither inhibitors of nor high affinity substrates for human liver cytochrome P450 isoforms, epoxide hydrolase or UDP glucuronidation enzymes.
Potential pharmacokinetic interactions assessed in clinical pharmacokinetic studies carried out indicated that levetiracetam does not influence the pharmacokinetics of phenytoin, valproate, carbamazepine, gabapentin, lamotrigine, phenobarbital and primidone and that these AEDs do not alter the pharmacokinetics of levetiracetam. In paediatric 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. Additional drug interactions assessed between levetiracetam and oral contraceptive, digoxin or warfarin indicate that levetiracetam does not influence the plasma concentration of these drugs and that these drugs do not influence the pharmacokinetics of levetiracetam. The effect of levetiracetam on probenecid was not studied. However probenecid did not affect the pharmacokinetics of levetiracetam.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Carcinogenesis

There is no evidence of carcinogenicity with levetiracetam. A study was conducted in which mice received levetiracetam in the diet for 80 weeks at doses of 60, 240 and 960 mg/kg/day. Although no evidence for carcinogenicity was seen, the potential for a carcinogenic response has not been fully evaluated in that species because adequate doses have not been studied.

Mutagenesis

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

Impairment of Fertility

No adverse effects on male or female fertility or reproductive performance were observed in rats at doses up to 1800 mg/kg/day (approximately 6 times the maximum recommended human dose on a mg/m2 or exposure basis).

Pregnancy

Pregnancy Category C
In animal studies, levetiracetam produced evidence of developmental toxicity at doses similar to or greater than human therapeutic doses. 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.

Nursing Mothers

Levetiracetam is excreted in breast 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.

Pediatric Use

Safety and effectiveness in patients below 4 years of age have not been established.

Geriatric Use

No overall differences in safety were observed between elderly subjects (60 years) and younger subjects. Levetiracetam is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug 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.

Use in 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 haemodialysis. The dosage of levetiracetam should be reduced in patients with impaired renal function and supplemental doses should be given to patients after dialysis.

ADVERSE REACTIONS

The most frequently reported adverse events associated with the use of levetiracetam in combination with other AEDs in adults were somnolence, asthenia, infection and dizziness. The adverse events most frequently reported with the use of levetiracetam in combination with other AEDs in paediatric patients were somnolence, accidental injury, hostility, nervousness and asthenia.
Of the most frequently reported adverse events in adults, asthenia, somnolence and dizziness are reported to occur predominantly during the first 4 weeks of treatment with levetiracetam.

Treatment-emergent adverse events occurred in at least 1% of Levetiracetam treated adults patients

Body as a Whole

Asthenia, headache, infection, pain

Digestive System

Anorexia

Nervous System

Amnesia, anxiety, ataxia, depression, dizziness, emotional lability, hostility, nervousness, paresthesia, somnolence, vertigo

Respiratory System

Cough increased, pharyngitis, rhinitis, sinusitis

Special Senses

Diplopia

Other events reported by 1% or more of adult patients treated with levetiracetam were the following: abdominal pain, accidental injury, amblyopia, arthralgia, back pain, bronchitis, chest pain, confusion, constipation, convulsion, diarrhea, drug level increased, dyspepsia, ecchymosis, fever, flu syndrome, fungal infection, gastroenteritis, gingivitis, grand mal convulsion, insomnia, nausea, otitis media, rash, thinking abnormal, tremor, urinary tract infection, vomiting and weight gain.

Treatment-emergent adverse events occurred in at least 2% of Levetiracetam treated pediatric patients (4-16 years).

Body as a Whole

Accidental injury, asthenia, pain, flu syndrome, face edema, neck pain, viral infection

Digestive System

Vomiting, anorexia, diarrhoea, gastroenteritis, constipation

Hemic and Lymphatic System

Ecchymosis

Metabolic and Nutritional

Dehydration

Nervous System

Somnolence, hostility, nervousness, personality disorder, dizziness, emotional ability, agitation, depression, vertigo, reflexes increased, confusion

Respiratory System

Rhinitis, cough increased, pharyngitis, asthma

Skin and Appendages

Pruritis, skin discoloration, vesiculobullous rash

Special Senses

Conjunctivitis, amblyopia, ear pain

Urogenital System

Albuminuria, urine abnormality

Other events occurring in 2% or more of pediatric patients treated with levetiracetam were the following: abdominal pain, allergic reaction, ataxia, convulsion, epistaxis, fever, headache, hyperkinesia, infection, insomnia, nausea, otitis media, rash, sinusitis, status epilepticus (not otherwise specified), thinking abnormal, tremor, and urinary incontinence.
The following adverse experiences have insufficient data to support an estimate of their incidence or to establish causation. Leukopenia, neutropenia, pancreatitis, thrombocytopenia, alopecia (recovery was observed in majority of cases where levetiracetam was discontinued). There have been reports of suicidal behaviour, including completed suicide.

DOSAGE AND ADMINISTRATION

Treatment should be initiated with a daily dose of 1000 mg/day, given as twice-daily dosing (500 mg BID). Additional dosing increments may be given (1000 mg/day additional every 2 weeks) to a maximum recommended daily dose of 3000 mg. Doses greater than 3000 mg/day have been used in open-label studies for periods of 6 months and longer. There is no evidence that doses greater than 3000 mg/day confer additional benefit.

Patients with Impaired Renal Function:

Recommended doses and adjustment for dose for adults are shown in table below. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in mL/min is needed. CLcr in mL/min may be estimated from serum creatinine (mg/dL) determination using the following formula:

$$CLcr = \frac{[140 - \text{age (years)}] \times \text{body weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

To account for females, CLcr determined from above equation should be multiplied by 0.85.

Creatinine clearance (mL/min)	Daily Dose	Dose Regimen (mg/day)
≥80	500-1500	Every 12h
50-80	500-1000	Every 12h
30-50	250-750	Every 12h
<30	250-500	Every 12h
ESRD patients on dialysis	50	Every 24h*

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

Paediatric Patients Ages 4 to <16 Years

Treatment should be initiated with a daily dose of 20 mg/kg in 2 divided doses (10 g/kg BID). 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 BID). If a patient cannot tolerate a daily dose of 60 mg/kg, the daily dose may be reduced. Patients with body weight ≤20 kg should be dosed with oral solution. Levetiracetam is given orally with or without food.

OVERDOSAGE

The highest known dose of levetiracetam received in the clinical studies was 6000 mg/day. Other than drowsiness, somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were also observed in cases of levetiracetam overdose.

STORAGE

STORE BELOW 30^{o}C

HOW SUPPLIED

Levetiracetam is available in blister pack of 10 tablets.

torrent PHARMA

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Baddi 173 205, Dist. Solan (H.P.) INDIA.