LEVETIRACETAM

Rx

LENTIRA

500 mg Film-Coated Tablet

ANTIEPILEPTIC

FORMULATION
Each film-coated tablet contains:
Levetiracetam ..... 500 mg

PRODUCT DESCRIPTION
White to off white, elongated, biconvex, plain on both side and film-coated tablets.

PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: antiepileptics, other antiepileptics
The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances.

Mechanism of action
The mechanism of action of levetiracetam still remains to be fully elucidated. In vitro and in vivo experiments suggest that levetiracetam does not alter basic cell characteristics and normal neurotransmission.
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.

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.

Clinical efficacy and safety
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 adults, levetiracetam efficacy has been demonstrated in 3 double-blind, placebo-controlled studies at 1000 mg, 2000 mg, or 3000 mg/day, given in 2 divided doses, with a treatment duration of up to 18 weeks. In a pooled analysis, the percentage of patients who achieved 50 % or greater reduction from baseline in the partial onset seizure frequency per week at stable dose (12/14 weeks) was of 27.7 %, 31.6 % and 41.3 % for patients on 1000, 2000 or 3000 mg levetiracetam respectively and of 12.6 % for patients on placebo.

PHARMACOKINETICS
Absorption of levetiracetam with peak plasma concentrations occurring in about an hour following oral administration in fasted subjects. The oral bioavailability of levetiracetam tablet is 100% and the tablet and oral solution are bioequivalent in rate and extent of absorption. Food does not affect the extent of absorption of levetiracetam but it decreases Cmax by 20% and delays Tmax by 1.5 hours. Levetiracetam is not extensively metabolized in humans. The major metabolic pathway is the enzymatic hydrolysis of the acetamide group, which produces the carboxylic acid, ucb L057 (24% of dose) and is not dependent on any liver cytochrome P450 isoenzymes. 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.

INDICATIONS
Levetiracetam is used as an adjunct in the treatment of partial seizures with or without secondary generalizations, myoclonic seizures, and primary generalized tonic-clonic seizures.

DOSAGE AND ADMINISTRATION
Partial Onset Seizures:
Adults 16 years and older-initial daily dose of 1000 mg/day given as twice-daily dosing (500 mg twice daily).
1 month to < 6 months-initial daily dose of 14 mg/kg in two divided doses (7 mg/kg twice daily).
6 months to < 4 years-initial 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 50mg/kg (25 mg/kg twice daily)
4 years to <16 years-initial 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 60mg/kg (30 mg/kg twice daily).

Myoclonic Seizures in patients 12 years of age 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.
Primary generalized tonic-clonic seizures:
Adult 16 years and older – treatments should be initiated with a dose of 1000 mg/day, given as twice-daily dosing (500 mg twice daily).
Pediatric patients ages 6 to < 16 years – treatment should be initiated with a daily dose of 20 mg/kg in 2 divided doses (10 mg/kg twice daily).

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

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
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.

220.00 mm

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 important weakness, pyrexia, recurrent infections or coagulation disorders.

Suicide
Suicide, suicide attempt, suicidal ideation and behaviour have been reported in patients treated with anti epileptic agents including levetiracetam. A meta-analysis of randomized placebo controlled trials of anti epileptic medicinal products has shown a small increased risk of suicidal thoughts and behaviour. The mechanism of this risk is not known.

Therefore, patients should be monitored for signs of depression and/or suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of depression and/or suicidal ideation or behaviour emerge.

Paediatric population
The tablet formulation is not adapted for use in infants and children under the age of 6 years.

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.

PRECAUTION
Levetiracetam should be used with caution and in reduced doses in patients with renal impairment, those undergoing haemodialysis and in patients with severe hepatic impairment.

Breast feeding: Levetiracetam is transferred into breast milk in significant amounts, but serum concentrations in breast-fed infants are very low.

Pregnancy: The management of epilepsy during pregnancy may present problems for both the mother and the fetus. Evidence for any effect of the newer antiepileptic on the fetus is particular scanty. Limited data have not so far suggested a significant increase in risk with levetiracetam.

ADVERSE DRUG REACTION
The most common adverse effects associated with levetiracetam are somnolence, weakness and dizziness. Anorexia, diarrhea, dyspepsia, nausea, ataxia, headache, amnesia, depression, emotional liability, insomnia, nervousness, tremor, vertigo, diplopia and rash may occur less frequently. A raised incidence of mild infections, such as the common cold and upper respiratory-tract infections has been reported.
Other effects reported include abnormal behavior, aggression, anger, anxiety, confusion, hallucinations, irritability, psychotic disorders, neutropenia, pancytopenia and thrombocytopenia.

DRUG INTERACTIONS
Potential pharmacokinetic interactions of or with levetiracetam were assessed in clinical pharmacokinetic studies (phenytoin, valproate, warfarin, digoxin, oral contraceptive, probenecid) and through pharmacokinetic screening in the placebo-controlled clinical studies in epilepsy patients. Symptoms of carbamazepine toxicity have been reported when levetiracetam was added to carbamazepine therapy; this interaction appeared to be due to pharmacodynamics mechanism as blood levels of carbamazepine and its metabolite were not altered.

OVERDOSE AND TREATMENT
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.

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph. Seek medical attention immediately at the first sign of any adverse drug reaction.

STORAGE CONDITION
Store at temperatures not exceeding 30ºC.
Keep all medicines out of reach of children.

AVAILABILITY
Alu/Alu Blister Pack x 10's (Box of 10's)

DRP-4583-02
Date of First Authorization: April 13, 2016
Date of Revision of Package Insert: August 14, 2023

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