Approved Package Insert for Levetiracetam Unicorn 250 & 750

SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

LEVETIRACETAM UNICORN 250 film coated tablets

LEVETIRACETAM UNICORN 750 film coated tablets

COMPOSITION

Active ingredient:

Each **LEVETIRACETAM UNICORN 250** tablet contains 250 mg levetiracetam.

Each **LEVETIRACETAM UNICORN 750** tablet contains 750 mg levetiracetam.

Inactive ingredients (for LEVETIRACETAM UNICORN 250 and LEVETIRACETAM UNICORN 750):

Croscarmellose sodium, magnesium stearate, polyethylene glycol, povidone and silica colloidal anhydrous.

LEVETIRACETAM UNICORN 250 contains Opadry Blue (containing FD&C blue No. 2, macrogol, polyvinyl alcohol, talc and titanium dioxide).

LEVETIRACETAM UNICORN 750 contains Opadry Orange (containing FD&C yellow No. 6, iron oxide red, macrogol, polyvinyl alcohol, talc and titanium dioxide).

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

Levetiracetam is an antiepileptic medicine. Levetiracetam is a pyrrolidone derivative, the *S*-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide, which is chemically unrelated to existing antiepileptic active substances.

The mechanism by which levetiracetam exert these antiseizure effects is unknown. No evidence for an action on voltage-gated Na^+ channels or either GABA- or glutamate-mediated synaptic transmission has emerged.

Pharmacokinetic properties:

Absorption:

Levetiracetam is well absorbed after oral administration, oral bioavailability is close to 100 %. Peak plasma concentrations (C_{max}) are achieved at 1,3 hours after dosing. Steady-state is achieved after 2 days of a twice daily administration schedule.

Plasma protein binding is minimal. Peak concentrations (C_{max}) are typically 31 and 43 µg/ml following a single 1 000 mg dose and repeated 1 000 mg dose respectively. The extent of absorption is dose-independent and is not altered by food.

Distribution:

The volume of distribution of levetiracetam is approximately 0,5 to 0,7 l/kg, a value close to the volume of distribution of intracellular and extracellular water.

Metabolism:

Levetiracetam neither induces nor is a high-affinity substrate for cytochrome P450 isoforms of glucuronidation enzymes and thus is devoid of known interactions with other antiseizure medicines, oral contraceptives or anticoagulants.

Elimination:

The plasma half-life in adults has been reported as 7 ± 1 hours. The total body clearance was a mean of 0,96 ml/min/kg. Approximately 95 % is excreted in the urine, 65 % of which is unchanged and 24 % is metabolised by hydrolysis of the acetamide group.

INDICATIONS

LEVETIRACETAM UNICORN is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and children over 16 years of age with epilepsy.

LEVETIRACETAM UNICORN is indicated as adjunctive therapy in the treatment of:

- Partial onset seizures with or without secondary generalisation in adults and children over 16 years of age with epilepsy.
- Myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy.
- Primary generalised tonic-clonic seizures in adults and adolescents from 16 years of age with idiopathic generalised epilepsy.

CONTRAINDICATIONS

Hypersensitivity to levetiracetam or other pyrrolidone derivatives or any of the other ingredients (see **COMPOSITION**).

Pregnancy and lactation (see **PREGNANCY AND LACTATION**).

WARNINGS AND SPECIAL PRECAUTIONS

Withdrawal of LEVETIRACETAM UNICORN therapy:

Withdrawal of **LEVETIRACETAM UNICORN** or transition to or from another type of antiepileptic therapy should be made gradually (e.g. 500 mg twice daily decrements every two to four weeks).

Patients with renal impairment:

Dose adjustment may be required for patients with renal impairment receiving **LEVETIRACETAM UNICORN** (see **DOSAGE AND DIRECTIONS FOR USE**).

Patients with hepatic impairment:

Prior to determining the dose of **LEVETIRACETAM UNICORN** for patients with severely impaired hepatic function, it is recommended that renal function should be assessed (see **DOSAGE AND DIRECTIONS FOR USE**).

Monitoring of plasma levels:

Plasma level monitoring of **LEVETIRACETAM UNICORN** is not required, due to the complete and linear absorption of levetiracetam. Plasma levels can be predicted from the oral dose of **LEVETIRACETAM UNICORN** expressed as mg/kg bodyweight.

Effects on the ability to drive vehicles or operate machinery:

Caution is recommended in patients performing skilled tasks, e.g. driving vehicles or operating machinery. At the beginning of treatment or after a dosage increase, some patients may experience somnolence or other CNS related symptoms.

INTERACTIONS

Potential interactions with existing antiepileptic medicines (such as phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) have not been demonstrated.

No interaction between probenecid and levetiracetam was observed, however, probenecid decreased the renal clearance of the inactive metabolite of levetiracetam by 60 %.
Co-administration of levetiracetam with digoxin, oral contraceptives or warfarin had no influence on the pharmacokinetics of levetiracetam.

PREGNANCY AND LACTATION

LEVETIRACETAM UNICORN is contraindicated in pregnancy. **LEVETIRACETAM UNICORN** is excreted in human breast milk. Patients using **LEVETIRACETAM UNICORN** should not breastfeed. (See **CONTRAINDICATIONS**.)

DOSAGE AND DIRECTIONS FOR USE

LEVETIRACETAM UNICORN should be taken orally, swallowed with liquid and may be taken with or without food. The daily dose is administered in two equally divided doses.

Monotherapy:

Adults and children from 16 years of age:

The recommended starting dose is 250 mg twice daily which should be increased to an initial therapeutic dose of 500 mg twice daily after two weeks. The dose can be further increased by 250 mg twice daily every two weeks depending upon the clinical response. The maximum daily dose is 1 500 mg twice daily.

Adjunctive therapy:

Adults (≥ 18 years) and adolescents (12 to 17 years) weighing 50 kg or more, when indicated:

As adjunctive therapy, the initial therapeutic dose is 500 mg twice daily. The dose can be started on the first day of treatment. Depending upon the clinical response and tolerance, the daily dose can be increased up to 1 500 mg twice daily. Dose changes can be made in 500 mg twice daily increments or decrements every two to four weeks.

Elderly (65 years and older):

Adjustment of the dose is recommended in elderly patients with compromised renal function (see **Patients with renal impairment** below).

Adolescents (12 to 17 years) weighing less than 50 kg, when indicated:

The initial therapeutic dose is 10 mg/kg twice daily. This dose can be started on the first day of treatment.

Depending upon the clinical response and tolerability the dose can be increased up to 30 mg/kg twice daily. Dose changes should not exceed increases or decreases of 10 mg/kg twice daily every two weeks. The lowest effective dose should be used.

Dosage in children 50 kg or greater is the same as in adults.

Infants and children less than 12 years:

There are insufficient data available for the use of **LEVETIRACETAM UNICORN** in children under the age of 12 years.

Patients with renal impairment:

The **LEVETIRACETAM UNICORN** dose should be individualised according to renal function. Refer to the table below and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CL_{cr}) in ml/min is needed. The CL_{cr} may be estimated from serum creatinine (mg/dl) determination using the following formula:

$$CL_{cr} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} \quad (\times 0{,}85 \text{ for women})$$

Dosing adjustment for patients with impaired renal function:

Group	Creatinine clearance (ml/min)	Dosage and frequency
Normal	> 80	500 to 1 500 mg twice daily
Mild	50 – 79	500 to 1 000 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[1]	___	500 to 1 000 mg once daily[2]
[1] A 750 mg loading dose is recommended on the first day of treatment with **LEVETIRACETAM UNICORN**.		

[2] Following dialysis, a 250 mg to 500 mg 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 < 70 ml/min.

SIDE EFFECTS

Infections and infestations:

Less frequent: Infection, nasopharyngitis.

Blood and lymphatic system disorders:

Frequency unknown: Leukopenia, neutropenia, pancytopenia, thrombocytopenia.

Endocrine disorders:

Frequency unknown: Pancreatitis.

Metabolism and nutrition disorders:

Frequent: Anorexia, weight increase.

Psychiatric disorders:

Frequent: Mood or mental changes, agitation, amnesia, anxiety, apathy, depersonalisation, depression, emotional lability, hostility, nervousness, aggression, insomnia, personality disorder, abnormal thinking.

Nervous system disorders:

Frequent: Dizziness, headache, somnolence, ataxia, convulsions, hyperkinesia, tremor, balance disorder, disturbances in attention, memory impairment.

Less frequent: Paraesthesia.

Eye disorders:

Frequent: Diplopia, blurred vision.

Ear and labyrinth disorders:

Frequent: Vertigo.

Respiratory, thoracic and mediastinal disorders:

Frequent: Pharyngitis, rhinitis, increased coughing.

Less frequent: Sinusitis.

Gastrointestinal disorders:

Frequent: Diarrhoea, dyspepsia, nausea, vomiting, abdominal pain.

Skin and subcutaneous tissue disorders:

Frequent: Alopecia, rash, eczema, pruritus.

Musculoskeletal, connective tissue and bone disorders:

Frequent: Myalgia.

General disorders:

Frequent: Asthenia, fatigue.

Injury and poisoning:

Frequent: Accidental injury.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms

Symptoms that may occur with **LEVETIRACETAM UNICORN** overdose includes: aggression, agitation, coma, depressed level of consciousness, respiratory depression, somnolence and drowsiness.

Treatment

There is no specific antidote for **LEVETIRACETAM UNICORN** overdose. Treatment should be symptomatic and supportive. Emesis or gastric lavage should be attempted if indicated. Standard haemodialysis should be considered, particularly, in selected patients based on clinical state of renal impairment. Approximately 50 % is removed in 4 hours.

IDENTIFICATION

LEVETIRACETAM UNICORN 250: Blue coloured, oblong shaped, film coated tablets, with a scoreline on one side and debossed with ‘250’ on the other side of the tablet.

LEVETIRACETAM UNICORN 750: Orange coloured, oblong shaped, film coated tablets, with a scoreline on one side and debossed with ‘750’ on the other side of the tablet.

PRESENTATION

LEVETIRACETAM UNICORN 250: Clear PVC/silver aluminium foil blister strips containing 10 tablets. Six blister strips (6 x 10) are packed in an outer cardboard box.

LEVETIRACETAM UNICORN 750: Clear PVC/silver aluminium foil blister strips containing 10 tablets. Six blister strips (6 x 10) are packed in an outer cardboard box.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Keep the blister strips in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

LEVETIRACETAM UNICORN 250: 46/2.5/0338

LEVETIRACETAM UNICORN 750: 46/2.5/0339

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Unicorn Pharmaceuticals (Pty) Ltd

Cnr. Searle & Pontac Streets

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8001

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