176 mm

252 mm

SM PHARMACEUTICALS SDN BHD

LEVISAT 500mg Film Coated Tablet

DESCRIPTION:
Yellow colored, oblong-shaped biconvex film coated tablet, debossed with "L" and "U" on either side of break line on one side and "X02" on the other side.

COMPOSITION:
Each film coated tablet contains:
Levetiracetam 500 mg

ACTIONS AND MODE OR MECHANISMS OF ACTION:
Mechanisms of Action:
The mechanism of action of levetiracetam still remains to be fully elucidated.
Clinical efficacy and safety
Adjunctive therapy in the treatment of partial onset seizures with or without secondary generalization in adults, adolescents and children from 4 years of age with epilepsy.

PHARMACOLOGY (SUMMARY OF PHARMACODYNAMICS AND PHARMACOKINETICS):
Pharmacodynamics
Pharmacotherapeutic group: antiepileptic's, 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.
Pharmacokinetics
Levetiracetam is a highly soluble and permeable compound. The pharmacokinetic profile is linear with low intra- and inter-subject variability. There is no modification of the clearance after repeated administration.
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. The extent of absorption is dose-independent and is not altered by food.
Distribution
Neither levetiracetam nor its primary metabolite are significantly bound to plasma proteins (< 10 %).
Metabolism
Levetiracetam is not extensively metabolized 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 P_{450} isoforms. Hydrolysis of the acetamide group was measurable in a large number of tissues including blood cells. The metabolite UCB L057 is pharmacologically inactive.
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 major route of excretion was through urine.
Renal impairment
The apparent body clearance of both Levetiracetam and of its primary metabolite is correlated to the creatinine clearance.

INDICATIONS:
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 generalisation 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-clonic seizures in adults and children from 12 years of age with Idiopathic Generalised Epilepsy.

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

SIDE EFFECTS / ADVERSE REACTIONS:

Classes	Frequency category			
	Very common	Common	Uncommon	Rare
Infections and infestations	Nasopharyngitis	-	-	Infection
Blood and lymphatic system disorders	-	-	Thrombocytopenia, leukopenia	Pancytopenia, neutropenia, agranulocytosis
Immune system disorders	-	-	-	Drug reaction with eosinophilia and systemic symptoms (DRESS), Hypersensitivity (including angioedema and anaphylaxis)
Metabolism and nutrition disorders	-	Anorexia	Weight decreased, weight increase	Hyponatraemia
Psychiatric disorders	-	Depression, hostility/ aggression, anxiety, insomnia, nervousness/irritability	Suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusional state , panic attack, affect lability/mood swings, agitation	Completed suicide, personality disorder, thinking abnormal, delirium
Nervous system disorders	Somnolence, headache	Convulsion, balance disorder, dizziness, lethargy, tremor	Amnesia, memory impairment, coordination abnormal/ataxia, paraesthesia, disturbance in attention	Choreoathetosis, dyskinesia, hyperkinesia, gait disturbance, encephalopathy
	Very common	Common	Uncommon	Rare
Ear and labyrinth disorders	-	Vertigo	-	-
Respiratory, thoracic and mediastinal disorders	-	Cough	-	-
Gastrointestinal disorders	-	Abdominal pain, diarrhoea, dyspepsia, vomiting, nausea	-	Pancreatitis
Hepatobiliary disorders	-	-	Liver function test abnormal	Hepatic failure, hepatitis
Renal and Urinary Disorders	-	-	-	Acute Kidney injury
Skin and subcutaneous tissue disorders	-	Rash	Alopecia, eczema, pruritus,	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme
Musculoskeletal and connective tissue disorders	-	-	Muscular weakness, myalgia	Rhabdomyolysis and blood creatine phosphokinase increased*
General disorders and administration site conditions	-	Asthenia/fatigue	-	-
Injury, poisoning and procedural complications	-	-	Injury	-

* Prevalence is significantly higher in Japanese patients when compared to non-Japanese patients.

Description of selected adverse reactions
•The risk of anorexia is higher when Levetiracetam is coadministered with topiramate.
•In several cases of alopecia, recovery was observed when Levetiracetam was discontinued.
•Bone marrow suppression was identified in some of the cases of pancytopenia.
•Cases of encephalopathy generally occurred at the beginning of the treatment (few days to a few months) and were reversible after treatment discontinuation.

PRECAUTIONS/WARNINGS:

Discontinuation
If levetiracetam has to be discontinued it is recommended to withdraw it gradually (e.g. in adults and adolescents weighing more than 50 kg: 500 mg decreases twice daily every two to four weeks; in children and adolescents weighing less than 50 kg: dose decrease should not exceed 10 mg/kg twice daily every two weeks).
Renal or hepatic 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.
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.
Depression and/or suicidal ideation
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 sign of depression and/or suicidal ideation or behaviour emerge.
Abnormal and aggressive behaviours
Levetiracetam may cause psychotic symptoms and behavioural abnormalities including irritability and aggressiveness. Patients treated with levetiracetam should be monitored for developing psychiatric signs suggesting important mood and/or personality changes. If such behaviours are noticed, treatment adaptation or gradual discontinuation should be considered. If discontinuation is considered, please see Section Discontinuation in Warnings and Precautions.
Paediatric population
The tablet formulation is not adapted for use in 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.

DRUG INTERACTIONS:

Antiepileptic medicinal products
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. As in adults, there is no evidence of clinically significant medicinal product interactions in pediatric patients receiving up to 60 mg/kg/day levetiracetam.
A retrospective assessment of pharmacokinetic interactions in children and adolescents with epilepsy (4 to 17 years) confirmed that adjunctive therapy with orally administered levetiracetam did not influence the steady-state serum concentrations of concomitantly administered carbamazepine and valproate. However, data suggested a 20 % higher levetiracetam clearance in children taking enzyme-inducing antiepileptic medicinal products. Dosage adjustment is not required.
Probenecid
Probenecid (500 mg 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.
Methotrexate
Concomitant administration of levetiracetam and methotrexate has been reported to decrease methotrexate clearance, resulting in increased/prolonged blood methotrexate concentration to potentially toxic levels. Blood methotrexate and levetiracetam levels should be carefully monitored in patients treated concomitantly with the two drugs
Oral contraceptives and other pharmacokinetics interactions
Levetiracetam 1,000 mg daily did not influence the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel); endocrine parameters (luteinizing hormone and progesterone) were not modified. Levetiracetam 2,000 mg daily did not influence the pharmacokinetics of digoxin and warfarin; prothrombin times were not modified. Co-administration with digoxin, oral contraceptives and warfarin did not influence the pharmacokinetics of Levetiracetam.
Laxatives
There have been isolated reports of decreased Levetiracetam efficacy when the osmotic laxative macrogol has been concomitantly administered with Levetiracetam. Therefore, macrogol should not be taken orally for one hour before and for one hour after taking levetiracetam.
Food and Alcohol
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.

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Effect on Ability to drive and use machine:
Levetiracetam has minor or moderate influence on the ability to drive and use machines. Due to possible different individual sensitivity, some patients might experience somnolence or other central nervous system related symptoms, especially at the beginning of treatment or following a dose increase. Therefore, caution is recommended in those patients when performing skilled tasks, e.g. driving vehicles or operating machinery. Patients are advised not to drive or use machines until it is established that their ability to perform such activities is not affected.

PREGNANCY AND LACTATION:
Women of child bearing potential
Advice should be given to women who are of childbearing potential. Treatment with Levetiracetam should be reviewed when a woman is planning to become pregnant. As with all antiepileptic medicines, sudden discontinuation of Levetiracetam should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child. Monotherapy should be preferred whenever possible because therapy with multiple antiepileptic medicines AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated antiepileptics.
Pregnancy
Levetiracetam can be used during pregnancy, if after careful assessment it is considered clinically needed. In such case, the lowest effective dose is recommended.
Physiological changes during pregnancy may affect Levetiracetam concentration. Decrease in levetiracetam plasma concentrations has been observed during pregnancy. Appropriate clinical management of pregnant women treated with Levetiracetam should be ensured.
Breastfeeding
Levetiracetam is excreted in human breast milk. Therefore, breast-feeding is not recommended. However, if Levetiracetam treatment is needed during breastfeeding, the benefit/risk of the treatment should be weighed considering the importance of breastfeeding.
Fertility
No impact on fertility was detected in animal studies. No clinical data are available, potential risk for human is unknown.

RECOMMENDED DOSAGE, DOSAGE SCHEDULE AND ROUTE OF ADMINISTRATION:
Levetiracetam therapy can be initiated with either intravenous or oral administration. Conversion to or from oral to intravenous administration can be done directly without titration. The total daily dose and frequency of administration should be maintained.
Film-coated tablets
The film-coated tablets must be taken orally, swallowed with a sufficient quantity of liquid and may be taken with or without food. After oral administration the bitter taste of levetiracetam may be experienced. The daily dose is administered in two equally divided doses.
Adults
Monotherapy
Adults and adolescents 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 dose is 1500 mg twice daily.
Add-on therapy
Adults (≥18 years) and adolescents (12 to 17 years) weighing 50 kg or more
The initial therapeutic dose is 500 mg 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 1,500 mg twice daily. Dose changes can be made in 500 mg twice daily increases or decreases every two to four weeks.
Children
The physician should prescribe the most appropriate pharmaceutical form, presentation and strength according to age, weight and dose.
The tablet formulation is not adapted for use in children under the age of 6 years. In addition, the available dose strengths of the tablets are not appropriate for initial treatment in children weighing less than 25 kg, for patients unable to swallow tablets or for the administration of doses below 250 mg.
Monotherapy
The safety and efficacy of levetiracetam in children and adolescents below 16 years as monotherapy treatment have not been established.
There are no data available.
Add-on therapy
Add-on therapy for children (4 to 11 years) and adolescents (12 to 17 years) weighing between 25 to 50 kg:
For children 6 years and above, levetiracetam tablet formulation is not adapted to be used for doses under 250 mg, for doses not multiple of 250 mg when dosing recommendation is not achievable by taking multiple tablets and for patients unable to swallow tablets.
The initial therapeutic dose is 10 mg/kg twice daily.
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.
Dose in children 50 kg or greater is the same as in adults.

Dose recommendations for children and adolescents:

Weight	Starting dose 10 mg/kg twice daily	Maximum dose 30 mg/kg twice daily
25 kg	250 mg twice daily	750 mg twice daily
From 50 kg (1)	500 mg twice daily	1500 mg twice daily

(1) Dose in children and adolescents 50 kg or more is the same as in adults
Children 25 kg or less should preferably start the treatment with levetiracetam 100 mg/ml oral solution

Elderly (65 years and older)
Adjustment of the dose is recommended in elderly patients with compromised renal function.

Renal impairment
The daily dose must be individualized 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, for adults and adolescents weighting 50 kg or more, using the following formula:

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

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

$$\text{CLcr (ml/min/1.73 m2)} = \frac{\text{CLcr (ml/min)}}{\text{BSA subject (m2)}} \times 1.73$$

Dosing adjustment for adult and adolescent patients weighing more than 50kg with impaired renal function

Group	Creatinine clearance (ml/min/1.73m2)	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 (1).	-	500 to 1000 mg once daily (2)

(1) A 750 mg loading dose is recommended on the first day of treatment with levetiracetam.
(2) Following dialysis, a 250 to 500 mg 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/1.73 m2 may be estimated from serum creatinine (mg/dl) determination using, for young adolescents and children using the following formula (Schwartz formula):

$$\text{CLcr (ml/min/1.73 m2)} = \frac{\text{Height (cm)} \times \text{ks}}{\text{Serum Creatinine (mg/dl)}}$$

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's patients weighing between 25 to 50 kg with impaired renal function

Group	Creatinine clearance (ml/min/1.73m2)	Children and adolescents weighing between 25 to 50 kg(1)
Normal	≥80	10 to 30 mg/kg twice daily
Mild	50-79	10 to 20 mg/kg twice daily
Moderate	30-49	5 to 15 mg/kg twice daily
Severe	< 30	5 to 10 mg/kg twice daily
End-stage renal disease patients undergoing dialysis	-	10 to 20 mg/kg once daily (2) (3)

(1) Levetiracetam tablet formulation is not adapted to be used for doses under 250 mg, for doses not multiple of 250 mg when dosing recommendation is not achievable by taking multiple tablets and for patients unable to swallow tablets.
(2) A 15 mg/kg loading dose is recommended on the first day of treatment with levetiracetam.
(3) Following dialysis, a 5 to 10 mg/kg supplemental dose is recommended.
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 < 60 ml/min/1.73m2.

SYMPTOMS AND TREATMENT FOR OVERDOSE AND ANTIDOTE(S):
Symptoms
Somnolence, agitation, aggression, depressed level of consciousness respiratory depression and coma were observed with Levetiracetam overdoses.
Management of overdose
There is no specific antidote for Levetiracetam. Treatment of an overdose will be symptomatic and may include haemodialysis. The dialyzer extraction efficiency is 60 % for levetiracetam and 74 % for the primary metabolite.

INSTRUCTION FOR USE:
The film-coated tablets must be taken orally, swallowed with a sufficient quantity of liquid and may be taken with or without food. After oral administration the bitter taste of Levetiracetam may be experienced. The daily dose is administered in two equally divided doses.

PACKING / PACK SIZES:
Blister Pack 10 x 10's tablets (Clear PVC/Aluminium foil)/Box.

STORAGE CONDITION:
Store below 30°C.

SHELF LIFE:
3 Years.

THERAPEUTIC CODE
N03AX14

NAME AND ADDRESS OF MANUFACTURER
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Lot 88, Sungai Petani Industrial Estate
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PRODUCT REGISTRATION HOLDER
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