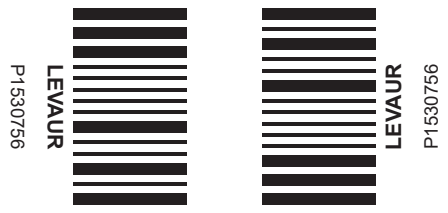
Pharmacode position may change as per Supplier's m/c requirement & additional small pharma code may appear on the front / back panel



SUMMARY OF PRODUCT CHARACTERISTICS

LEVAUR

Levetiracetam Tablets 250 mg, 500 mg

NAME OF THE MEDICINAL PRODUCT : Levetiracetam Tablets 250 mg.
Levetiracetam Tablets 500 mg.

(TRADE) NAME OF PRODUCT : LEVAUR 250.
LEVAUR 500.

STRENGTH : 250 mg, 500 mg.

QUALITATIVE AND QUANTITATIVE COMPOSITION
Levetiracetam Tablets 250 mg: Each film-coated tablet contains 250 mg Levetiracetam.
Levetiracetam Tablets 500 mg: Each film-coated tablet contains 500 mg Levetiracetam.

PHARMACEUTICAL FORM
Levetiracetam Tablets 250 mg: Blue oval shaped biconvex film -coated tablets debossed with a deep break line separating 'E' and '10' on one side and plain on the other side.
Levetiracetam Tablets 500mg: Yellow oval shaped biconvex film -coated tablets debossed with a deep break line separating 'E' and '11' on one side and plain on the other side.

CLINICAL PARTICULARS
Therapeutic indications
Levetiracetam is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation 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 adolescents from 12 years of age with Idiopathic Generalised Epilepsy.

Posology and method of administration
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. 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. Levetiracetam oral solution is the preferred formulation for use in this population. 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. In all of the above cases levetiracetam oral solution should be used.

- **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 less than 50 kg
Levetiracetam oral solution is the preferred formulation for use in children under the age of 6 years.

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
10 kg (1)	100 mg (1 ml) twice daily	300 mg (3 ml) twice daily
15 kg (1)	150 mg (1.5 ml) twice daily	450 mg (4.5 ml) twice daily
20 kg (1)	200 mg (2 ml) twice daily	600 mg (6 ml) twice daily
25 kg	250 mg twice daily	750 mg twice daily
From 50 kg (2)	500 mg twice daily	1500 mg twice daily

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

Elderly
Adjustment of the dose is recommended in elderly patients with compromised renal function.

Renal impairment
The daily dose must be individualised according to renal function *(see Section Warnings and Precautions)*.

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:

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

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

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

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):

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

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 adolescents patients weighing less than 50 kg with impaired renal function

Dosing adjustment for children and adolescents patients weighing less than 50kg with impaired renal function

Group	*Creatinine clearance (ml/min/1.73m²)*	*Children and adolescents weighing less than 50 kg*
Normal	> 80	10 to 30 mg/kg (0.10 to 0.30 ml/kg) twice daily
Mild	50-79	10 to 20 mg/kg (0.10 to 0.20 ml/kg) twice daily
Moderate	30-49	5 to 15 mg/kg (0.05 to 0.15 ml/kg) twice daily
Severe	< 30	5 to 10 mg/kg (0.05 to 0.10 ml/kg) twice daily
End-stage renal disease patients undergoing dialysis	-	10 to 20 mg/kg (0.10 to 0.20 ml/kg)once daily (2) (3)

(1) Levetiracetam oral solution should 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 (0.15 ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.
(3) Following dialysis, a 5 to 10 mg/kg (0.05 to 0.10 ml/kg) 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 < 60 ml/min/1.73m^2.

Route of Administration
Oral.

Contraindications
Hypersensitivity to Levetiracetam or other pyrrolidone derivatives or 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.

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.

Effects on ability to drive and use machines.

No studies on the effects on the ability to drive and use machines have been performed. Due to possible different individual sensitivity, some patients might experience, somnolence or other central nervous system related symptoms, 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.

Interaction with other medicinal products and other forms of interaction
Levetiracetam do 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 do not influence the pharmacokinetics of Levetiracetam.

As in adults, clinically significant medicinal product interactions in paediatric patients receiving up to 60 mg/kg/day Levetiracetam are none known.

The adjunctive therapy with orally administered Levetiracetam do not influence the steady-state serum concentrations of concomitantly administered carbamazepine and valproate. Dosage adjustment is not required.

Probenecid (500 mg four times daily), a renal tubular secretion blocking agent, inhibit the renal clearance of the primary metabolite but not of Levetiracetam. Nevertheless, the concentration of this metabolite remains low. It is expected that other medicinal products excreted by active tubular secretion could also reduce the renal clearance of the metabolite.

The effect of Levetiracetam on other actively secreted medicinal products, *e.g.* NSAIDs, sulfonamides and methotrexate, is unknown.

Levetiracetam 1,000 mg daily do not influence the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel) and endocrine parameters (luteinizing hormone and progesterone). Levetiracetam 2,000 mg daily do not influence the pharmacokinetics of digoxin and warfarin; prothrombin times were not modified. Co-administration with digoxin, oral contraceptives and warfarin do not influence the pharmacokinetics of Levetiracetam.

The extent of absorption of Levetiracetam is not altered by food, but the rate of absorption slightly reduced.

There is no interaction of Levetiracetam with alcohol.

Pregnancy and lactation
The potential risk for human is unknown.

Pregnancy:
Levetiracetam should not be used during pregnancy unless clearly necessary. As with other antiepileptic drugs, physiological changes during pregnancy may affect Levetiracetam concentration. Discontinuation of antiepileptic treatments may result in exacerbation of the disease which could be harmful to the mother and the foetus.

Lactation:
Levetiracetam is excreted in human breast milk. Therefore, breastfeeding 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.

Undesirable effects:
Summary of the safety profile

A/s: 280 x 390 mm ■ Black Booklet Size: 35 x 60 mm

AUROBINDO Packaging Development		Product Name	Component	Item Code	Date & Time
		Levaur Tablets	Leaflet	P1530756	25.02.2025 & 12.50 pm
		Country	Version No.	Reason Of Issue	Reviewed / Approved by
		Malaysia Unit-15	03	Submission	
Team Leader	Kiran Kumar	Dimensions (mm)	Colours: 01		
Initiator	Shirisha N	A/s: 280 x 390 mm			
Artist	Advnt (Aman)	Pharma Code: 30756			
Additional Information: Supersede Code: P1518015					

The most frequently reported adverse reactions were nasopharyngitis, somnolence, headache, fatigue and dizziness. The safety profile of levetiracetam is generally similar across age groups (adult and paediatric patients) and across the approved epilepsy indications.

Tabulated list of adverse reactions

Adverse reactions reported and from post marketing experience are listed in the following table per System Organ Class and per frequency. Adverse reactions are presented in the order of decreasing seriousness.

MedDRA SOC	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
Nervous system disorders	Somnolence, headache	Convulsion, balance disorder, dizziness, lethargy, tremor	Amnesia, memory impairment, coordination abnormal/ataxia, paraesthesia, disturbance in attention	Choreoathetosis, dyskinesia, hyperkinesia
Eye disorders			Diplopia, vision blurred	
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.

Cases of encephalopathy have been rarely observed after levetiracetam administration. These undesirable effects generally occurred at the beginning of the treatment (few days to a few months) and were reversible after treatment discontinuation.

Description of selected adverse reactions

The risk of anorexia is higher when levetiracetam is co-administered 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.

Paediatric population

In patients aged 1 month to less than 4 years, data are supplemented with the post-marketing experience of the use of levetiracetam. No new safety concerns for levetiracetam were identified for infants less than 12 months of age with epilepsy.

The adverse reaction profile of levetiracetam is generally similar across age groups and across the approved epilepsy indications. Safety results in paediatric patients were consistent with the safety profile of levetiracetam in adults except for behavioural and psychiatric adverse reactions which were more common in children than in adults. In children and adolescents aged 4 to 16 years, vomiting, agitation, mood swings, affect liability, aggression, abnormal behaviour and lethargy were reported more frequently than in other age ranges or in the overall safety profile. In infants and children aged 1 month to less than 4 years, irritability and coordination abnormal were reported more frequently than in other age groups or in the overall safety profile.

Overdose

Symptoms

Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma.

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.

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: 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 but appears to be different from the mechanisms of current antiepileptic medicinal products. *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 release. 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 animals of partial and primary generalised seizures without having a pro-convulsant effect. The primary metabolite is inactive.

Pharmacokinetic properties

The pharmacokinetic profile has been characterized following oral administration. A single dose of 1500 mg Levetiracetam diluted in 100 ml of a compatible diluent and infused intravenously over 15 minutes is bioequivalent to 1500 mg Levetiracetam oral intake, given as three 500 mg tablets.

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. The time independent pharmacokinetic profile of Levetiracetam was also confirmed following 1500 mg intravenous infusion for 4 days with b.i.d. dosing.

Due to its complete and linear absorption, plasma levels can be predicted from the oral dose of Levetiracetam expressed as mg/kg bodyweight. Therefore there is no need for plasma level monitoring of Levetiracetam.

Adults and adolescents

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

Distribution

No tissue distribution data are available in humans.

Neither Levetiracetam nor its primary metabolite are significantly bound to plasma proteins (< 10 %).

The volume of distribution of Levetiracetam is approximately 0.5 to 0.7 l/kg, a value close to the total body water volume.

Biotransformation

Levetiracetam is not extensively metabolised 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.

Levetiracetam shows two minor metabolites, one is by hydroxylation of the pyrrolidone ring (1.6 % of the dose) and the other one by opening of the pyrrolidone ring (0.9 % of the dose).

Other unidentified components accounted only for 0.6 % of the dose.

In vitro, Levetiracetam and its primary metabolite does not inhibit the major human liver cytochrome P_{450} isoforms (CYP3A4, 2A6, 2C9, 2C8/9/10, 2C19, 2D6, 2E1 and 1A2), glucuronyl transferase (UGT1A1 AND UGTIA6) and epoxide hydroxylase activities. In addition, Levetiracetam does not affect the *in vitro* glucuronidation of valproic acid.

Elimination

The plasma half-life in adults is 7±1 hours and does not vary either with dose, route of administration or repeated administration. The mean total body clearance was 0.96 ml/min/kg.

The major route of excretion via urine, accounting for a mean 95 % of the dose. Excretion *via* faeces accounted for only 0.3 % of the dose.

The cumulative urinary excretion of Levetiracetam and its primary metabolite accounted for 66 % and 24 % of the dose, respectively during the first 48 hours.

The renal clearance of Levetiracetam is 0.6 indicating that Levetiracetam is excreted by glomerular filtration with subsequent tubular reabsorption.

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 in this population.

Children (4 to 12 years)

Pharmacokinetics in adults after intravenous administration and the pharmacokinetics in children after oral administration, the exposure (AUC) of Levetiracetam is expected to be similar in paediatric patients aged 4-12 years after intravenous and oral administration.

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.

Hepatic impairment

In severe hepatic impairment, the clearance of levetiracetam is reduced by more than 50 % due to a concomitant renal impairment.

PHARMACEUTICAL PARTICULARS

List of excipients

Levetiracetam Tablets 250 mg:
Maize Starch, Silica Collodial anhydrous, Povidone, Talc, Magnesium Stearate, Opadry Blue

Levetiracetam Tablets 500 mg:
Maize Starch, Silica Collodial anhydrous, Povidone, Talc, Magnesium Stearate, Opadry Yellow

Incompatibilities

None known.

Shelf life

Please refer outer package for expiry date.

Special precautions for storage

Do not store above 30°C.

Nature and contents of container

Blister Pack: Blister of 10 tablets.

Manufactured By:

AUROBINDO

AUROBINDO PHARMA LTD.,
Unit-XV, Plot No.17 A, E- Bonangi Village,Jawaharlal Nehru Pharma City,
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53300 Kuala Lumpur, Malaysia.

DATE OF PREPARATION OF THIS LEAFLET
February-2025

P1530756