SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF DRUG PRODUCT

Leveget (Levetiracetam) Tablets 250mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Levetiracetam USP...250mg

3. PHARMACEUTICAL FORM

Light orange colored, oblong shaped, biconvex film coated table, plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Leveget (Levetiracetam) Tablet is indicated as:
Monotherapy:
• in the treatment of partial onset seizures with or without secondary generalization in adults and adolescents from 16 years of age with newly diagnosed epilepsy.

Adjunctive Therapy:
• in the treatment of partial onset seizures with or without secondary generalization in adults, adolescents and childrens 6 years of age or above 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 generalized tonic-clonic seizures in adults and adolescents from 6 years of age with Idiopathic Generalized Epilepsy.

4.2 Posology and method of administration

Leveget (Levetiracetam) is given with or without food. The dosage regimens depends on the indication, age group, dosage form & renal function. The tablets should be swallowed whole and not be chewed or crushed.

Monotherapy for adults and adolescents from 16 years of age
The recommended starting dose is 250mg twice daily which should be increased to an initial therapeutic dose of 500mg twice daily after two weeks. The dose can be further increased by 250mg twice daily every two weeks depending upon the clinical response. The maximum dose is 1500mg twice daily.

Dosing for Partial Onset Seizures

Adults 16 Years and Older
Initiate treatment with a daily dose of 1000mg/day, given as twice-daily dosing (500mg twice daily). Additional dosing increments may be given (1000mg/day additional every 2 weeks) to a maximum recommended daily dose of 3000mg. There is no evidence that doses greater than 3000mg/day confer additional benefit**.**

Pediatric Patients (6 Years to < 16 Years)
Initiate treatment with a daily dose of 20mg/kg in 2 divided doses (10mg/kg twice daily). Increase the daily dose every 2 weeks by increments of 20mg/kg to the recommended daily dose of 60mg/kg (30mg/kg twice daily). If a patient cannot tolerate a daily dose of 60mg/kg, the daily dose may be reduced. In the clinical trial, the mean daily dose was 44mg/kg. The maximum daily dose was 3000mg/day**.**

For Leveget (Levetiracetam) Tablet, dosing in pediatric patients weighing 20kg to 40kg, initiate treatment with a daily dose of 500mg given as twice daily dosing (250mg twice daily). Increase the daily dose every 2 weeks by increments of 500mg to a maximum recommended daily dose of 1500mg (750mg twice daily).

For Leveget (Levetiracetam) Tablet, dosing in pediatric patients weighing more than 40kg, initiate treatment with a daily dose of 1000mg/day given as twice daily dosing (500mg twice daily). Increase the daily dose every 2 weeks by increments of 1000mg/day to a maximum recommended daily dose of 3000mg (1500mg twice daily).

Dosing for Myoclonic Seizures in Patients 12 Years of Age and Older with Juvenile Myoclonic Epilepsy
Initiate treatment with a dose of 1000mg/day, given as twice-daily dosing (500mg twice daily). Increase the dosage by 1000mg/day every 2 weeks to the recommended daily dose of 3000mg. The effectiveness of doses lower than 3000mg/day has not been studied.

Dosing for Primary Generalized Tonic-Clonic Seizures
Adults 16 Years and Older
Initiate treatment with a dose of 1000mg/day, given as twice-daily dosing (500mg twice daily). Increase dosage by 1000mg/day every 2 weeks to the recommended daily dose of 3000mg. The effectiveness of doses lower than 3000mg/day has not been adequately studied**.**

Pediatric Patients (Ages 6 to <16 Years)
Initiate treatment with a daily dose of 20mg/kg in 2 divided doses (10mg/kg twice daily).
Increase the daily dose every 2 weeks by increments of 20mg/kg to the recommended daily dose of 60mg/kg (30mg/kg twice daily). The effectiveness of doses lower than 60mg/kg/day has not been adequately studied**.**

Discontinuation
If Leveget (Levetiracetam) has to be discontinued it is recommended to withdraw it gradually(e.g. in adults and adolescents weighing more than 50kg: 500mg decreases twice daily every two to four weeks; in children and adolescents weighting less than 50kg: dose decrease should not exceed 10mg/kg twice daily every two weeks)

Special Population

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.

Dosing adjustment for adult and adolescents patients with impaired renal function.

Group	**Creatinine Clearance (ml/min/1.73m^2)**	**Creatinine Clearance (ml/min/1.73m^2)**
Normal	>80	500mg to 1500mg twice daily
Mid	50-79	500 to 1000mg twice daily
Moderate	30-49	250 to 750mg twice daily
Severe	<30	250 to 500mg twice daily
End-stage renal disease patients undergoing dialysis[1]	-	500-1000 once daily[2]

[1]A 750mg loading dose is recommended on the first day of treatment with levetiracetam.
[2] Following dialysis, a 250mg to 500mg 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.

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

Group	**Creatinine Clearance (ml/min/1.73m^2)**	**Dosage and frequency**
		Children and adolescents weighing less than 50 kg
Normal	>80	10mg to 30m/kg twice daily
Mid	50-79	10 to 20mg/kg twice daily
Moderate	30-49	5mg to 15mg/kg twice daily
Severe	<30	5mg to 10mg/kg twice daily
End-stage renal disease patients undergoing dialysis	-	10mg to 20mg/kg once daily[1] [2]

[1] Following dialysis, a 3.5 to 7mg/kg supplemental dose is recommended.
[2] Following dialysis, a 5 to 10mg/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 < 60mL/min/1.73m^2.

Pediatric population
Monotherapy
The safety & efficacy of levetiracetam in children and adolescents below 16 years as monotherapy treatment have not been established.

Add-on therapy for children (6 to 11 years) and adolescents (12 to 17 years) weighing less than 50kg.
The lowest effective dose should be used. The starting dose for a child or adolescent of 25kg should be 250mg twice daily with a maximum dose of 750mg twice daily.
Dose in children 50kg or greater is the same as in adults

4.3 Contraindications

Levetiracetam is contraindicated in patients who are hypersensitive to the active substance or other pyrrolidone derivatives or to any excipient of the product.

4.4 Special warnings and special 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 significant weakness, pyrexia, recurrent infections or coagulation disorders.

Suicide
Antiepileptic drugs (AEDs), including levetiracetam, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Anaphylaxis and Angioedema
Levetiracetam can cause anaphylaxis or angioedema after the first dose or at any time during treatment. If a patient develops signs or symptoms of anaphylaxis or angioedema, levetiracetam should be discontinued and the patient should seek immediate medical attention. Levetiracetam should be discontinued permanently if a clear alternative etiology for the reaction cannot be established.

Serious Dermatological Reactions
Serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in both pediatric and adult patients treated with levetiracetam. The median time of onset is reported to be 14 to 17 days, but cases have been reported at least four months after initiation of treatment. Recurrence of the serious skin reactions following rechallenge with levetiracetam has also been reported. Levetiracetam should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered.

Withdrawal Seizures
Antiepileptic drugs, including levetiracetam, should be withdrawn gradually to minimize the potential of increased seizure frequency.

Somnolence and Fatigue
Levetiracetam may cause somnolence, fatigue, coordination difficulties. Patients should be monitored for these signs and symptoms and advised not to drive or operate machinery until they have gained sufficient experience on levetiracetam to gauge whether it adversely affects their ability to drive or operate machinery.

Seizure Control During Pregnancy
Physiological changes may gradually decrease plasma levels of levetiracetam throughout pregnancy. This decrease is more pronounced during the third trimester. It is recommended that patients be monitored carefully during pregnancy. Close monitoring should continue through the postpartum period especially if the dose was changed during pregnancy.

4.5 Interaction with other medicaments and other forms of interaction

Probenecid
Renal clearance of ucb L057 in the presence of probenecid decreased 60%, probably related to competitive inhibition of tubular secretion of ucb.

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.

Laxatives
There have been isolated reports of decreased levetiracetam efficacy when the osmotic laxative macrogol has been concomitantly administered with oral levetiracetam. Therefore, macrogol

should not be taken orally for one hour before and for one hour after taking levetiracetam

4.6 Uses in Pregnancy and Lactation

Pregnancy
There are no adequate and controlled studies in pregnant women. In animal studies, levetiracetam produced evidence of developmental toxicity, including teratogenic effects, at doses similar to or greater than human therapeutic doses. Levetiracetam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Levetiracetam is excreted in human 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

4.7 Effects on ability to drive and operate machines

Levetiracetam has minor or moderate influence on the ability to drive and use machines. Therefore caution is recommended. Patients are advised not to drive or use machines until it is established that their ability to perform such activities is not affected.

4.8 Undesirable effects

The following adverse reactions have been reported during the use of Levetiracetam:

Very common: Nasopharyngitis, somnolence and headache.

Common: Anorexia, depression, hostility/aggression, anxiety, insomnia, nervousness/irritability, convulsion, balance disorder, dizziness, lethargy, tremor, vertigo, cough, abdominal pain, diarrhoea, dyspepsia, vomiting, nausea, rash and asthenia/fatigue.

Uncommon: Thrombocytopenia, leucopenia, weight decrease, weight increase, suicide attempt and suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusional state, panic attack, emotional instability/mood swings, agitation, amnesia, memory impairment, abnormal coordination/ataxia, paraesthesia, disturbance in attention, diplopia, vision blurred, liver function test abnormal, alopecia, eczema, pruritus, muscle weakness, myalgia and injury.

Rare: Infection, pancytopenia, neutropenia, agranulocytopenia, drug reaction with eosinophilia and systemic symptoms (DRESS), hypersensitivity, hyponatraemia, completed suicide, personality disorder, thinking abnormal, hepatic failure, hepatitis, acute kidney injury, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, rhabdomyolysis and blood creatinine phosphokinase increased.

4.9 OVERDOSAGE

The highest known dose of levetiracetam received in the clinical development program was 6000mg/day. Other than drowsiness, there were no adverse reactions in the few known cases

of overdose in clinical trials. Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with levetiracetam overdoses in post-marketing use.

Management of overdose
There is no specific antidote for overdose with levetiracetam. If indicated, elimination of unabsorbed drug should be attempted by emesis or gastric lavage; usual precautions should be observed to maintain airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the patient's clinical status.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacokinetic properties

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 1000mg dose and repeated 1000mg twice daily dose, respectively. The pharmacokinetics of levetiracetam are linear over the dose range of 500mg - 5000mg.

Effect of Food
Food does not affect the extent of absorption of levetiracetam but it decreases C_{max} by 20% and delays T_{max} by 1.5 hours. 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.

Metabolism
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 P450 isoforms. Hydrolysis of the acetamide group was measurable in a large number of tissues including blood cells. The metabolite ucb L057 is pharmacologically inactive. Two minor metabolites were also identified.
One was obtained 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). No enantiomeric interconversion was evidenced in vivo for either levetiracetam or its primary metabolite

Elimination
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. The total body clearance is 0.96mL/min/kg and the renal clearance is 0.6mL/min/kg. The mechanism of excretion is glomerular filtration with subsequent partial tubular reabsorption. The metabolite ucb L057 is excreted by glomerular filtration and active tubular secretion with a renal clearance of 4mL/min/kg. Levetiracetam elimination is correlated to creatinine clearance. Levetiracetam clearance is reduced in patients with renal impairment.

Special Population

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.

Renal impairment

The disposition of levetiracetam was studied in adult subjects with varying degrees of renal function. Total body clearance of levetiracetam is reduced in patients with impaired renal function by 40% in the mild group (CLcr = 50-80mL/min), 50% in the moderate group (CLcr =30-50mL/min) and 60% in the severe renal impairment group (CLcr <30mL/min). Clearance of levetiracetam is correlated with creatinine clearance.

In anuric (end stage renal disease) patients, the total body clearance decreased 70% compared to normal subjects (CLcr > 80mL/min). Approximately 50% of the pool of levetiracetam in the body is removed during a standard 4- hour hemodialysis procedure.

Hepatic impairment

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

Pediatric population

Children (6 to 12 years)

Following single oral dose administration (20mg/kg) to epileptic children (6 to 12 years), the half-life of levetiracetam was 6 hours. The apparent body weight adjusted clearance was approximately 30% higher than in epileptic adults.

Following repeated oral dose administration (20 to 60mg/kg/day) to epileptic children (4 to 12 years), levetiracetam was rapidly absorbed. Peak plasma concentration was observed 0.5 to1.0 hour after dosing. Linear and dose proportional increases were observed for peak plasma concentration and area under the curve. The elimination half-life was approximately 5 hours.The apparent body clearance was 1.1mL/min/kg.

Gender

Levetiracetam C_{max} and AUC were 20% higher in women (N=11) compared to men (N=12).However, clearances adjusted for body weight were comparable.

5.2 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in Antiepileptic **ATC code:** N03AX14

The mechanism of action of levetiracetam still remains to be fully elucidated. 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.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential.

Adverse effects not observed in clinical studies but seen in the rat and to a lesser extent in the mouse at exposure levels similar to human exposure levels and with possible relevance for clinical use were liver changes, indicating an adaptive response such as increased weight and centrilobular hypertrophy, fatty infiltration and increased liver enzymes in plasma.

No adverse reactions on male or female fertility or reproduction performance were observed in rats at doses up to 1800 mg/kg/day (x 6 the MRHD on a mg/m2 or exposure basis) in parents and F1 generation.

Two embryo-foetal development (EFD) studies were performed in rats at 400, 1200 and 3600 mg/kg/day. At 3600 mg/kg/day, in only one of the 2 EFD studies, there was a slight decrease in foetal weight associated with a marginal increase in skeletal variations/minor anomalies. There was no effect on embryomortality and no increased incidence of malformations. The NOAEL (No Observed Adverse Effect Level) was 3600 mg/kg/day for pregnant female rats (x 12 the MRHD on a mg/m2 basis) and 1200 mg/kg/day for fetuses.

Four embryo-foetal development studies were performed in rabbits covering doses of 200, 600, 800, 1200 and 1800 mg/kg/day. The dose level of 1800 mg/kg/day induced a marked maternal toxicity and a decrease in foetal weight associated with increased incidence of foetuses with cardiovascular/skeletal anomalies. The NOAEL was <200 mg/kg/day for the dams and 200 mg/kg/day for the fetuses (equal to the MRHD on a mg/m2 basis).

A peri- and post-natal development study was performed in rats with levetiracetam doses of 70, 350 and 1800 mg/kg/day. The NOAEL was ≥ 1800 mg/kg/day for the F0 females, and for the survival, growth and development of the F1 offspring up to weaning (x 6 the MRHD on a mg/m2 basis).

Neonatal and juvenile animal studies in rats and dogs demonstrated that there were no adverse effects seen in any of the standard developmental or maturation endpoints at doses up to 1800 mg/kg/day (x 6 – 17 the MRHD on a mg/m^2 basis).

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

P.E.G 6000 (Macrogol), Croscarmellose Sodium, Aerosil 200, Magnesium Stearate, Purified Talc, Purified Water, Opadry II Orange 85F38005

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

2 Years
The expiration dates refers to the product correctly stored in the required conditions.

6.4 Special precautions for storage

- Do not store above 30°C.
- Protect from light & moisture.
- The expiration date refers to the product correctly stored at the required conditions.

6.5 Nature and contents of container

Leveget (Levetiracetam) Tablets 250mg are available in Alu-PVC blister pack of 3×10's in a unit carton along with the package insert.

6.6 Special precautions for disposal

No special requirements.

6.7 Instructions for use/handling

Keep out of reach of children.
To be dispensed on prescription only.

7. MARKETING AUTHORISATION HOLDER

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8. DATE OF REVISION OF THE TEXT

Nil

9. PRODUCT REGISTRATION NUMBER

007326-EX

10. DATE OF PRODUCT REGISTRATION ISSUED

August 06, 2018