Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Leveget 250mg film coated tablets
Leveget 500mg film coated tablets

2. Qualitative and quantitative composition

Leveget 500mg film coated tablets
Each film-coated tablet contains 500mg of Levetiracetam
Leveget 250mg film coated tablets
Each film-coated tablet contains 250mg of Levetiracetam

3. Pharmaceutical form

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

4. Clinical particulars

4.1 Therapeutic indications

Leveget is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy.
Leveget is indicated as 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 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.

4.2 Posology and method of administration

Posology

Monotherapy for 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 for 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.

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 infants older than 6 months, children and adolescents weighting less than 50 kg: dose decrease should not exceed 10 mg/kg twice daily every two weeks; in infants (less than 6 months): dose decrease should not exceed 7 mg/kg twice daily every two weeks).

Special populations

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 individualised 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, the following formula:

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

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

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

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

Group	Creatinine clearance (ml/min/1.73m^2)	Dose and frequency
Normal	≥ 80	500 to 1,500 mg twice daily
Mild	50-79	500 to 1,000 mg twice daily
Modera te	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.
(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 m^2 may be estimated from serum creatinine (mg/dl) determination, for young adolescents, children and infants, using the following formula (Schwartz formula):

$$CL_{cr}\ (ml/min/1.73\ m^2) = \frac{Height\ (cm) \times ks}{Serum\ Creatinine\ (mg/dl)}$$

ks= 0.45 in Term infants to 1 year old; ks= 0.55 in Children to less than 13 years and in adolescent female; ks= 0.7 in adolescent male

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

Group	Creatinine clearance (ml/min/1.73 m^2)	Dose and frequency (1)	
		Infants 1 to less than 6 months	Infants 6 to 23 months, children and adolescents weighing less than 50 kg
Normal	≥ 80	7 to 21 mg/kg (0.07 to 0.21 ml/kg) twice daily	10 to 30 mg/kg (0.10 to 0.30 ml/kg) twice daily
Mild	50-79	7 to 14 mg/kg (0.07 to 0.14 ml/kg) twice daily	10 to 20 mg/kg (0.10 to 0.20 ml/kg) twice daily
Moderate	30-49	3.5 to 10.5 mg/kg (0.035 to 0.105 ml/kg) twice daily	5 to 15 mg/kg (0.05 to 0.15 ml/kg) twice daily
Severe	< 30	3.5 to 7 mg/kg (0.035 to 0.07 ml/kg) twice daily	5 to 10 mg/kg (0.05 to 0.10 ml/kg) twice daily
End-stage renal disease patients undergoing dialysis	--	7 to 14 mg/kg (0.07 to 0.14 ml/kg) once daily (2) (4)	10 to 20 mg/kg (0.10 to 0.20 ml/kg) once daily (3) (5)

(1) Leveget 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 10.5 mg/kg (0.105 ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.
(3) A 15 mg/kg (0.15 ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.
(4) Following dialysis, a 3.5 to 7 mg/kg (0.035 to 0.07 ml/kg) supplemental dose is recommended.
(5) Following dialysis, a 5 to 10 mg/kg (0.05 to 0.10 ml/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/1.73 m^2.

Paediatric population

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 infants and children under the age of 6 years. Leveget 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 Leveget oral solution should be used.

Monotherapy

The safety and efficacy of Leveget in children and adolescents below 16 years as monotherapy treatment have not been established.

No data are available.

Add-on therapy for infants aged from 6 to 23 months, children (2 to 11 years) and adolescents (12 to 17 years) weighing less than 50 kg

Leveget oral solution is the preferred formulation for use in infants and children under the age of 6 years.

For children 6 years and above, Leveget 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

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 50 kg or greater is the same as in adults.

Add-on therapy for infants aged from 1 month to less than 6 months

The oral solution is the formulation to use in infants.

Method of administration

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.

4.3 Contraindications

Hypersensitivity to the active substance or other pyrrolidone derivatives or to any of the excipients listed in section 6.1

4.4 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 (section 4.8).

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.

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 refer to section 4.2.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Antiepileptic medicinal products

Pre-marketing data from clinical studies conducted in adults indicate that 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 paediatric 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. Dose 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 oral 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.

4.6 Pregnancy and Lactation

Women of child bearing potential

Specialist 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. This decrease is more pronounced during the third trimester (up to 60% of baseline concentration before 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.

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

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 creatine phosphokinase increased*.
* 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.

MedDRA SOC	Frequency category

	Very Common	Common	Uncommon	Rare	Very 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,	Completed suicide, personality disorder, thinking abnormal, delirium	Obsessive compulsive disorder**

Reporting of Adverse Drug Reactions
Healthcare professionals are asked to report any suspected adverse drug reactions via the Pharmacy and Poisons Board's; Pharmacovigilance-Electronic-Reporting-System(PvERS)
https://pv.pharmacyboardkenya.org/

4.9 Overdose

Symptoms

Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with Leveget 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**.**

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiepileptics, other antiepileptics, ATC code: N03AX14.
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 Ca2+ levels by partial inhibition of N- type Ca2+ currents and by reducing the release of Ca2+ 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

5.2 Pharmacokinetic properties

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. There is no evidence for any relevant gender, race or circadian variability. The pharmacokinetic profile is comparable in healthy volunteers and in patients with epilepsy.
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.
A significant correlation between saliva and plasma concentrations has been shown in adults and children (ratio of saliva/plasma concentrations ranged from 1 to 1.7 for oral tablet formulation and after 4 hours post-dose for oral solution formulation).

Adults and adolescents Absorption
Levetiracetam is rapidly absorbed after oral administration. Oral absolute bioavailability is close to 100 %. Peak plasma concentrations (Cmax) are achieved at 1.3 hours after dosing. Steady-state is achieved after two days of a twice daily administration schedule. Peak concentrations (Cmax) 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 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). Other unidentified components accounted only for 0.6 % of the dose. No enantiomeric interconversion was evidenced in vivo for either levetiracetam or its primary metabolite.
In vitro, levetiracetam and its primary metabolite have been shown not to inhibit the major human liver cytochrome P450 isoforms (CYP3A4, 2A6, 2C9, 2C19, 2D6, 2E1 and 1A2), glucuronyl

transferase (UGT1A1 AND UGT1A6) and epoxide hydroxylase activities. In addition, levetiracetam does not affect the in vitro glucuronidation of valproic acid.
In human hepatocytes in culture, levetiracetam had little or no effect on CYP1A2, SULT1E1 or UGT1A1. Levetiracetam caused mild induction of CYP2B6 and CYP3A4. The in vitro data and in vivo interaction data on oral contraceptives, digoxin and warfarin indicate that no significant enzyme induction is expected in vivo. Therefore, the interaction of Leveget with other substances, or vice versa, is unlikely.

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 mean total body clearance was 0.96 ml/min/kg.
The major route of excretion was via urine, accounting for a mean 95 % of the dose (approximately 93 % of the dose was excreted within 48 hours). 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 and ucb L057 is 0.6 and 4.2 ml/min/kg respectively indicating that levetiracetam is excreted by glomerular filtration with subsequent tubular reabsorption and that the primary metabolite is also excreted by active tubular secretion in addition to glomerular filtration. Levetiracetam elimination is correlated to creatinine clearance.

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 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 Leveget, based on creatinine clearance in patients with moderate and severe renal impairment.
In anuric end-stage renal disease adult subjects the half-life was approximately 25 and 3.1 hours during interdialytic and intradialytic periods, respectively. The fractional removal of levetiracetam was 51 % during a typical 4-hour dialysis session.

Hepatic impairment
In subjects with mild and moderate hepatic impairment, there was no relevant modification of the clearance of levetiracetam. In most subjects with severe hepatic impairment, the clearance of

levetiracetam was reduced by more than 50 % due to a concomitant renal impairment

5.3 Preclinical safety data

Paediatric population

Children (4 to 12 years)

Following single oral dose administration (20 mg/kg) to epileptic children (6 to 12 years), the half- life of levetiracetam was 6.0 hours. The apparent body weight adjusted clearance was approximately 30 % higher than in epileptic adults.

Following repeated oral dose administration (20 to 60 mg/kg/day) to epileptic children (4 to 12 years), levetiracetam was rapidly absorbed. Peak plasma concentration was observed 0.5 to 1.0 hour after dosing. Linear and dose proportional increases were observed for peak plasma concentrations and area under the curve. The elimination half-life was approximately 5 hours. The apparent body clearance was 1.1 ml/min/kg.

Infants and children (1 month to 4 years)

Following single dose administration (20 mg/kg) of a 100 mg/ml oral solution to epileptic children (1 month to 4 years), levetiracetam was rapidly absorbed and peak plasma concentrations were observed approximately 1 hour after dosing. The pharmacokinetic results indicated that half-life was shorter (5.3 h) than for adults (7.2 h) and apparent clearance was faster (1.5 ml/min/kg) than for adults (0.96 ml/min/kg).

In the population pharmacokinetic analysis conducted in patients from 1 month to 16 years of age, body weight was significantly correlated to apparent clearance (clearance increased with an increase in body weight) and apparent volume of distribution. Age also had an influence on both parameters. This effect was pronounced for the younger infants, and subsided as age increased, to become negligible around 4 years of age.

In both population pharmacokinetic analyses, there was about a 20 % increase of apparent clearance of levetiracetam when it was co-administered with an enzyme-inducing antiepileptic medicinal product.

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 1,800mg/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, 1,200 and 3,600 mg/kg/day. At 3,600mg/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 embryo mortality and no increased incidence of malformations. The NOAEL (No Observed Adverse Effect Level) was 3,600 mg/kg/day for pregnant female rats (x 12 the MRHD on a mg/m2 basis) and 1,200 mg/kg/day for fetuses.

Four embryo-foetal development studies were performed in rabbits covering doses of 200, 600, 800, 1,200 and 1,800mg/kg/day. The dose level of 1,800 mg/kg/day induced a marked maternal toxicity and a decrease in foetal weight associated with increased incidence of fetuses 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 1,800 mg/kg/day. The NOAEL was ≥ 1,800 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 1,800 mg/kg/day (x 6-17 the MRHD on a mg/m2 basis).

6. Pharmaceutical Particulars

6.1 List of Excipients

- P.E.G 6000 (Macrogol)
- Croscarmellose Sodium
- Colloidal Anhydrous Silica (Aerosil 200)
- Magnesium Stearate
- Opadry II Orange 85F38005

6.2 Incompatibilities

N/A

6.3 Shelf-Life

2 years

6.4 Special Precautions for storage

- Do not store above 30°C.
- Protect from light and moisture.
- Keep out of reach of children.

6.5 Nature and Content of container

Leveget (Levetiracetam) Tablets 500mg and 250mg are available in Alu - PVC blister pack of 10's packed in a printed unit carton along with the package insert.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder

Getz Pharma (Private) Limited
29-30/27, Korangi Industrial Area Karachi 74900, Pakistan Tel: (92-21) 5063100-03
Fax: (92-21) 5060141

8. Marketing Authorization Number

Leveget 250mg tablets- CTD9250
Leveget 500mg tablets-CTD9248

9. Date of first authorization/renewal of the authorization

Leveget 250mg tablets- 18/04/2023
Leveget 500mg tablets- 23/08/2024

10. Date of revision of the text

13/05/2025