SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of drug product

Leveget (Levetiracetam) IV 500mg/5mL

2. Qualitative and quantitative composition

Each 5ml ampoule contains:
Levetiracetam USP...500mg
Excipient with known effect:
5ml of solution for injection contains 17.68mg sodium

2. Pharmaceutical form

Clear colorless transparent liquid filled in clear glass USP Type I ampoule

4. Clinical particulars

4.1. Indications

LEVEGET (Levetiracetam) IV 500mg/5ml is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from16 years of age with newly diagnosed epilepsy.
LEVEGET (Levetiracetam) IV 500mg/5ml is indicated as adjunctive therapy
• in the treatment of partial onset seizures with or without secondary generalisation in adults,adolescents and children from 4 years of age with epilepsy.
• in the treatment of myoclonic seizures in adults and adolescents from 12 years of age withJuvenile Myoclonic Epilepsy.
• in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from12 years of age with Idiopathic Generalised Epilepsy.

4.2. Posology and method 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.

Partial onset seizures

The recommended dosing for monotherapy (from 16 years of age) and adjunctive therapy is the same; as outlined below.

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. However, a lower initial dose of 250 mg twice daily may be given based on physician assessment of seizure reduction versus potential side effects. This can be increased to 500 mg twice daily after two weeks.

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 250 mg or 500 mg twice daily increases or decreases every two to four weeks.

Adolescents (12 to 17 years) weighing below 50 kg and children from 1 month of age

The physician should prescribe the most appropriate pharmaceutical form, presentation and strength according to weight, age and dose. Refer to Paediatric population section for dosing adjustments based on weight.

Duration of treatment

There is no experience with administration of intravenous levetiracetam for longer period than4 days.

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).

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 weighing 50 kg or more, the following formula:

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

Then CL_{cr} is adjusted for body surface area (BSA) as follows:

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

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

Group	**Creatinine Clearance (ml/ min/1.73m2)**	**Dose and frequency**
Normal	> 80	500 to 1,500 mg twice daily

Mild	50-79	500 to 1,000 mg twicedaily
Moderate	30-49	250 to 750 mg twicedaily
Severe	< 30	250 to 500 mg twice daily
End-stage renal diseasepatients undergoing dialysis (1)	-	500 to 1,000 mg oncedaily(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 renalfunction 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, for young adolescents and children using the following formula (Schwartz formula):

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

Dosing adjustment for children and adolescent patients weighing less than 50 kg with impairedrenal function:

Group	**Creatinine Clearance (ml/min/ 1.73m2)**	**Dose and frequency**
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 undergoingdialysis (1)	-	10 to 20 mg/kg (0.10 to 0.20 ml/kg) once daily (1) (2)

(1) A 15 mg/kg (0.15 ml/kg) loading dose is recommended on the first day of treatment withlevetiracetam.

(2) 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.

Monotherapy

The safety and efficacy of Leveget IV in children and adolescents 16 years as monotherapy treatment have not been established initial therapeutic dose is 10 mg/kg twice daily.

Adolescents (16 and 17 years of age) weighing 50 kg or more with partial onset seizureswith or without secondary generalisation with newly diagnosed epilepsy

Please refer Adults (≥18 years) and adolescents (12 to 17 years) weighing 50 kg or more.

Add-on therapy for children aged 4 to 11 years and adolescents (12 to 17 years) weighing less than 50 kg

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 for all indications. Dose in children 50 kg or greater is the same as in adults for all indications.

Please refer to the above section on Adults (≥18 years) and adolescents (12 to 17 years) weighing 50 kg or more for all Indication.

Weight	**Starting dose: 10 mg/kg twice daily**	**Maximum dose: 30 mg/kg twice daily**
15 kg (1)	150 mg twice daily	450 mg twice daily
15 kg (1)	200 mg twice daily	600 mg twice daily
15 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 Leveget 100 mg/ml oral solution.

(2) Dose in children and adolescents 50 kg or more is the same as in adults.

Add-on therapy for infants and children less than 4 years

The safety and efficacy of Leveget concentrate for solution for infusion in infants and childrenless than 4 years have not been established.

Method of administration

Leveget concentrate is for intravenous use only and the recommended dose must be diluted in at least 100 ml of a compatible diluent and administered intravenously as a 15-minute intravenous infusion

4.3. Contra-indications

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 isrecommended before dose selection

Acute Kidney Injury

The use of levetiracetam has been very rarely associated with acute kidney injury, with a timeto 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
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.

Worsening of seizures
As with other types of antiepileptic drugs, levetiracetam may rarely exacerbate seizure frequency or severity. This paradoxical effect was mostly reported within the first month after levetiracetam initiation or increase of the dose, and was reversible upon drug discontinuation or dose decrease. Patients should be advised to consult their physician immediately in case of aggravation of epilepsy

Electrocardiogram QT interval prolongation
Rare cases of ECG QT interval prolongation have been observed during the post-marketing surveillance. Levetiracetam should be used with caution in patients with QTc-interval prolongation, in patients concomitantly treated with drugs affecting the QTc-interval, or in patients with relevant pre-existing cardiac disease or electrolyte disturbances.

Pediatric Population
Available data in children did not suggest impact on growth and puberty. However, long term effects on learning, intelligence, growth, endocrine function, puberty and child bearing potential in children remain unknown.

Excipients
This medicinal product contains 2.5 mmol (or 57 mg) sodium per maximum single dose (0.8 mmol (or 19 mg) per vial). To be taken into consideration by patients on a controlled sodium diet.

4.5. Interaction with other medicaments 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.

Probenecid
Probenecid (500mg four times daily) 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.

Alcohol
No data on the interaction of levetiracetam with alcohol are available

4.6. Use in Pregnancy

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There are no adequate and controlled studies in pregnant women.
Levetiracetam should beused 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.

Fertility
No impact on fertility was detected in animal studies (see section 5.3). 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. Dueto 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, leukopenia, weight decrease, weight increase, suicide attempt and suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusional state, panic attack, affect lability/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, agranulocytosis, drug reaction with eosinophilia and systemic symptoms (DRESS), hypersensitivity (including angioedema and anaphylaxis, hyponatraemia, completed suicide, personality disorder, thinking abnormal, choreoathetosis, dyskinesia, hyperkinesia, gait disturbance, encephalopathy, seizures aggravated,

Electrocardiogram QT prolonged, pancreatitis, hepatic failure, hepatitis, acute kidney injury, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, rhabdomyolysis and blood creatine phosphokinase increased.

4.9. Overdose

Symptoms
Somnolence, agitation, aggression, depressed level of consciousness, respiratorydepression 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 dialyser extraction efficiency is 60% for levetiracetam and 74% for the primary metabolite.

5.PHARMACOLOGICAL PROPERTIES

1. Pharmacodynamic

properties Mechanism of

Action

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 additionit 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.

2. Pharmakokinetic properties

Absorption:
The pharmacokinetic profile has been characterized following oral administration.A single dose of 1500mg levetiracetam diluted in 100ml of a compatible diluent and infused intravenously over 15 minutes is bioequivalent to 1500mg levetiracetam oral intake, given as three 500mg tablets.
The intravenous administration of doses up to 4000mg diluted in 100ml of 0.9% sodium chloride infused over 15 minutes and doses up to 2500mg diluted in 100ml of 0.9% sodium chloride infused over 5 minutes was evaluated.The pharmacokinetic and safety profiles did not identify any safety concerns.
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.

Distribution

Peak plasma concentration (C_{max}) observed in 17 subjects following a single intravenous dose of 1500mg infused over 15 minutes was 51±19 µg/ml. 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 metabolized in humans. The major metabolic pathway is the enzymatic hydrolysis of the acetamide group, which produces the carboxylic acid metabolite, ucb L057 (24% of dose) and is not dependent on any liver cytochrome P450 isoenzymes. The major metabolite is inactive in animal seizure models. Two minor metabolites were identifiedas the product of hydroxylation of the 2-oxo-pyrrolidine ring (2% of dose) and opening of the 2-oxo-pyrrolidine ring in position 5 (1% of dose). There is no enantiomeric interconversion of levetiracetam or its major 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 metaboliteucb L057 is excreted by glomerular filtration and active tubular secretion with a renalclearance 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 (CL_{cr} = 50-80ml/min), 50% in the moderate group (CL_{cr}
= 30-50ml/min) and 60% in the severe renal impairment group (CL_{cr} <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 (CL_{cr}

>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

Paediatric population

Children (4 to 12 years)
The pharmacokinetics in paediatric patients has not been investigated after intravenous administration. However, based on the pharmacokinetic characteristics of levetiracetam, the 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 to 12 years after intravenous and oral administration.
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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
- Sodium Chloride
- Sodium Acetate Trihydrate
- Acetic Acid
- Water for Injection

6.2. Incompatibilities
Not applicable.

6.3. Shelf-life
2 years
The expiration date refers to the product correctly stored in the required conditions.

6.4. Special precautions for storage
- Do not store above 30°C.

- Protect from sunlight.
- The diluted solution should not be stored for more than 4 hours at controlled room temperature (15°C – 30°C)

6.5. Nature and contents of container

Leveget IV (Levetiracetam) Injection 500mg/5ml is available in clear glass USP Type 1 ampoule pack of 1's.

6.6. Special precautions for disposal and other handling

- Keep out of reach of children.
- To be sold on prescription of a registered medical practitioner only.
- The diluted solution should not be stored for more than 4 hours at controlled room temperature (15°C – 30°C)

7. Marketing authorisation holder

Getz Pharma (Private) Limited
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Fax: (92-21) 5060141

Manufacturing address.

Getz pharma (pvt) ltd
29-30 sector 27,korangi industrial area karachi-74900, pakistan.

8. Marketing authorisation number

H2024/CTD10531/17845

9. Date of first authorisation:

16/02/2024

10. Date of revision of the text:

November 2024