

## SUMMARY PRODUCTS CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

AEPISETEM

Levetiracetam Injection USP, 100 mg/mL (5 mL)

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

#### *Qualitative declaration*

Levetiracetam USP

#### *Quantitative declaration*

Each ml contains 100 mg of Levetiracetam USP.

Each 5 ml vial contains 500 mg of Levetiracetam USP.

#### Excipient with known effect:

Each 5 ml vial contains 19 mg of Sodium.

For the full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Solution for Injection

Clear Colourless Solution.

### 4. CLINICAL PARTICULARS

#### *4.1 Therapeutic indications*

**Levetiracetam** Injection 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.

- 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 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*

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.

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 ( $\geq 18$  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.

### **Duration of treatment**

There is no experience with administration of intravenous levetiracetam for longer period than 4 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 (see "Renal impairment" below).

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:

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

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

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

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

<b>Group</b>	<b>Creatinine clearance (ml/min/1.73m<sup>2</sup>)</b>	<b>Dose and frequency</b>
Normal	> 80	500 to 1,500 mg twice daily
Mild	50-79	500 to 1,000 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 <sup>(1)</sup>	-	500 to 1,000 mg once daily <sup>(2)</sup>

<sup>(1)</sup> A 750 mg loading dose is recommended on the first day of treatment with Levetiracetam.

<sup>(2)</sup> 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 CL<sub>Cr</sub> in ml/min/1.73 m<sup>2</sup> may be estimated from serum creatinine (mg/dl) determination, for young adolescents and children using the following formula (Schwartz formula):

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

ks= 0.55 in Children to less than 13 years and in adolescent female; ks= 0.7 in adolescent male

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

<b>Group</b>	<b>Creatinine clearance (ml/min/1.73m<sup>2</sup>)</b>	<b>Dose and frequency Children from 4 years and adolescents weighing less than 50 kg</b>
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 <sup>(1) (2)</sup>

<sup>(1)</sup> A 15 mg/kg (0.15 ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.

(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<sup>2</sup>.

### **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 Levetiracetam concentrate for solution for infusion in children below and adolescents 16 years as monotherapy treatment have not been established.

No data are available.

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.

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

Dose recommendations for children and adolescents:

<b>Weight</b>	<b>Starting dose: 10 mg/kg twice daily</b>	<b>Maximum dose: 30 mg/kg twice daily</b>
15 kg <sup>(1)</sup>	150 mg twice daily	450 mg twice daily
20 kg <sup>(1)</sup>	200 mg twice daily	600 mg twice daily
25 kg	250 mg twice daily	750 mg twice daily
From 50 kg <sup>(2)</sup>	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.

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

The safety and efficacy of Levetiracetam concentrate for solution for infusion in infants and children less than 4 years have not been established.

Currently available data are described in sections 4.8, 5.1, and 5.2 but no recommendation on a posology can be made.

### **Method of administration**

Levetiracetam concentrate for solution for infusion 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 Contraindications***

Hypersensitivity to the active substance or other pyrrolidone derivatives

#### **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 (see section 4.2).

##### *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.

##### *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.

##### *Paediatric 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 childbearing 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 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.

### *Alcohol*

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

## **4.6 Fertility, pregnancy and lactation**

### *Women of child bearing potential*

Specialist advice should be given to women who are of child bearing 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*

A large amount of postmarketing data on pregnant women exposed to levetiracetam monotherapy (more than 1,800, among which in more than 1500 exposure occurred during the 1st trimester) do not suggest an increase in the risk for major congenital malformations. Only limited evidence is available on the neurodevelopment of children exposed to levetiracetam monotherapy in utero. However, current epidemiological studies (on about 100 children) do not suggest an increased risk of neurodevelopmental disorders or delays. Levetiracetam can be used during pregnancy, if after careful assessment it is considered clinically needed. In such case, the lowest cost 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 (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. 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**

#### *Summary of the safety profile*

The most frequently reported adverse reactions were nasopharyngitis, somnolence, headache, fatigue and dizziness. The adverse reaction profile presented below is based on the analysis of pooled placebo-controlled clinical trials with all indications studied, with a total of 3,416 patients treated with levetiracetam. These data are supplemented with the use of levetiracetam in corresponding open-label extension studies, as well as post-marketing experience. The safety profile of levetiracetam is generally similar across age groups (adult and paediatric patients) and across the approved epilepsy indications. Since there was limited exposure for Levetiracetam intravenous use and since oral and intravenous formulations are bioequivalent, the safety information of Levetiracetam intravenous will rely on Levetiracetam oral use.

#### *Tabulated list of adverse reactions*

Adverse reactions reported in clinical studies (adults, adolescents, children and infants > 1 month) 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 and their frequency is defined as follows: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ) and very rare ( $< 1/10,000$ ).

MedDRA SOC	Frequency category			
	Very common	Common	Uncommon	Rare
Infections and infestations	Nasopharyngitis			Infection

MedDRA SOC	Frequency category			
	Very common	Common	Uncommon	Rare
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, gait disturbance

MedDRA SOC	Frequency category			
	Very common	Common	Uncommon	Rare
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		

MedDRA SOC	Frequency category			
	Very common	Common	Uncommon	Rare
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 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.

### *Paediatric population*

In patients aged 1 month to less than 4 years, a total of 190 patients have been treated with levetiracetam in placebo-controlled and open label extension studies. Sixty of these patients were treated with levetiracetam in placebo-controlled studies. In patients aged 4-16 years, a total of 645 patients have been treated with levetiracetam in placebo-controlled and open label extension studies. 233 of these patients were treated with levetiracetam in placebo-controlled studies. In both these paediatric age ranges, these data are supplemented with the post-marketing experience of the use of levetiracetam.

In addition, 101 infants aged less than 12 months have been exposed in a post authorization safety study. 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 in placebo-controlled clinical studies 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 (very common, 11.2%), agitation (common, 3.4%), mood swings (common, 2.1%), affect lability (common, 1.7%), aggression (common, 8.2%), abnormal behaviour (common, 5.6%), and lethargy (common, 3.9%) 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 (very common, 11.7%) and coordination abnormal (common, 3.3%) were reported more frequently than in other age groups or in the overall safety profile.

A double-blind, placebo-controlled paediatric safety study with a non-inferiority design has assessed the cognitive and neuropsychological effects of levetiracetam in children 4 to 16 years of age with partial onset seizures. It was concluded that levetiracetam was not

different (non inferior) from placebo with regard to the change from baseline of the Leiter-R Attention and Memory, Memory Screen Composite score in the per-protocol population. Results related to behavioural and emotional functioning indicated a worsening in levetiracetam treated patients on aggressive behaviour as measured in a standardised and systematic way using a validated instrument (CBCL – Achenbach Child Behavior Checklist). However subjects, who took levetiracetam in the long-term open label follow-up study, did not experience a worsening, on average, in their behavioural and emotional functioning; in particular measures of aggressive behaviour were not worse than baseline.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product, Healthcare professionals are asked to report any suspected adverse reactions to **TMDA**

### **4.9 Overdose**

#### *Symptoms*

Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with levetiracetam concentrate for solution for infusion 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**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: antiepileptics, other antiepileptics, ATC code: N03AX14.

The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of  $\alpha$ -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 Ca<sup>2+</sup> levels by partial inhibition of N-type Ca<sup>2+</sup> currents and by reducing the release of Ca<sup>2+</sup> from intraneuronal stores. In addition, it partially reverses the reductions in GABA- and glycine-gated currents induced by zinc and  $\beta$ -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 analogues 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 animal models of partial and primary generalised seizures without having a pro-convulsant effect. The primary metabolite is inactive.

In man, an activity in both partial and generalised epilepsy conditions (epileptiform discharge/photo paroxysmal response) has confirmed the broad-spectrum pharmacological profile of levetiracetam.

### **Clinical efficacy and safety**

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 adults, levetiracetam efficacy has been demonstrated in 3 double-blind, placebo-controlled studies at 1000 mg, 2000 mg, or 3000 mg/day, given in 2 divided doses, with a treatment duration of up to 18 weeks. In a pooled analysis, the percentage of patients who achieved 50 % or greater reduction from baseline in the partial onset seizure frequency per week at stable dose (12/14 weeks) was of 27.7 %, 31.6 % and 41.3 % for patients on 1000, 2000 or 3000 mg levetiracetam respectively and of 12.6 % for patients on placebo.

### **Paediatric population**

In paediatric patients (4 to 16 years of age), levetiracetam efficacy was established in a double-blind, placebo-controlled study, which included 198 patients and had a treatment duration of 14 weeks. In this study, the patients received levetiracetam as a fixed dose of 60 mg/kg/day (with twice a day dosing).

44.6 % of the levetiracetam treated patients and 19.6 % of the patients on placebo had a 50 % or greater reduction from baseline in the partial onset seizure frequency per week. With continued long-term treatment, 11.4 % of the patients were seizure-free for at least 6 months and 7.2 % were seizure-free for at least 1 year.

35 infants aged less than 1 year with partial onset seizures have been exposed in placebo-control clinical studies of which only 13 were aged < 6 months.

Monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy.

Efficacy of levetiracetam as monotherapy was established in a double-blind, parallel group, non-inferiority comparison to carbamazepine-controlled release (CR) in 576 patients 16 years of age or older with newly or recently diagnosed epilepsy. The patients had to present with unprovoked partial seizures or with generalized tonic-clonic seizures only. The patients

were randomized to carbamazepine CR 400 – 1200 mg/day or levetiracetam 1000 – 3000 mg/day, the duration of the treatment was up to 121 weeks depending on the response.

Six-month seizure freedom was achieved in 73.0 % of levetiracetam-treated patients and 72.8 % of carbamazepine-CR treated patients; the adjusted absolute difference between treatments was 0.2% (95 % CI: -7.8 8.2). More than half of the subjects remained seizure free for 12 months (56.6 % and 58.5 % of subjects on levetiracetam and on carbamazepine CR respectively).

In a study reflecting clinical practice, the concomitant antiepileptic medication could be withdrawn in a limited number of patients who responded to levetiracetam adjunctive therapy (36 adult patients out of 69).

Adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.

Levetiracetam efficacy was established in a double-blind, placebo-controlled study of 16 weeks duration, in patients 12 years of age and older suffering from idiopathic generalized epilepsy with myoclonic seizures in different syndromes. The majority of patients presented with juvenile myoclonic epilepsy.

In this study, levetiracetam, dose was 3000 mg/day given in 2 divided doses.

58.3 % of the levetiracetam treated patients and 23.3 % of the patients on placebo had at least a 50 % reduction in myoclonic seizure days per week. With continued long-term treatment, 28.6 % of the patients were free of myoclonic seizures for at least 6 months and 21.0 % were free of myoclonic seizures for at least 1 year.

Adjunctive therapy in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalised epilepsy.

Levetiracetam efficacy was established in a 24-week double-blind, placebo-controlled study which included adults, adolescents and a limited number of children suffering from idiopathic generalized epilepsy with primary generalized tonic-clonic (PGTC) seizures in different syndromes (juvenile myoclonic epilepsy, juvenile absence epilepsy, childhood absence epilepsy, or epilepsy with Grand Mal seizures on awakening). In this study, levetiracetam dose was 3000 mg/day for adults and adolescents or 60 mg/kg/day for children, given in 2 divided doses.

72.2 % of the levetiracetam treated patients and 45.2 % of the patients on placebo had a 50 % or greater decrease in the frequency of PGTC seizures per week. With continued long-term treatment, 47.4 % of the patients were free of tonic-clonic seizures for at least 6 months and 31.5 % were free of tonic-clonic seizures for at least 1 year.

## **5.2 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.

The intravenous administration of doses up to 4000 mg diluted in 100 ml of 0.9 % sodium chloride infused over 15 minutes and doses up to 2500 mg diluted in 100 ml 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. The time independent pharmacokinetic profile of levetiracetam was also confirmed following 1500 mg intravenous infusion for 4 days with twice daily dosing.

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.

#### *Adults and adolescents*

##### *Distribution*

Peak plasma concentration (C<sub>max</sub>) observed in 17 subjects following a single intravenous dose of 1500 mg infused over 15 minutes was 51 ± 19 µg/ml (arithmetic average ± standard deviation).

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 Levetiracetam with other substances, or vice versa, is unlikely.

#### *Elimination*

The plasma half-life in adults was  $7 \pm 1$  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 (see section 4.2).

#### *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 concentrate for solution for infusion, based on creatinine clearance in patients with moderate and severe renal impairment (see section 4.2).

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.

#### *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.

### **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/m<sup>2</sup> 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/m<sup>2</sup> 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 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/m<sup>2</sup> 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/m<sup>2</sup> 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<sup>2</sup> basis).

## **6. PHARMACEUTICAL PARTICULARS**

### 6.1 List of excipients

Sodium acetate trihydrate USP

Glacial acetic acid USP

Sodium chloride USP

Water for injections USP

### 6.2 Incompatibilities

Levetiracetam concentrate for solution for infusion was found to be chemically and physically stable and compatible when mixed with the following diluents for at least 24 hours and stored in PVC bags or PP bottles under controlled temperature of 25 °C.

- Sodium chloride 9 mg/ml (0.9%) solution for injection, USP
- Hartmann's or Ringer's lactate solution for injection
- Dextrose 50 mg/ml (5%) solution for injection, USP

### 6.3 Shelf life

2 years

### 6.4 Special precautions for storage

Do not store above 30°C. Keep vial in the outer carton in order to protect from light.

### 6.5 Nature and contents of container

5 ml clear glass vial (type I) closed by a grey Bromo butyl rubber stopper and sealed with an aluminium flip off cap. Vials are packed as pack of 10 or 25 in a single carton with package insert.

### 6.6 Special precautions for disposal <and other handling>

See below table for the recommended preparation and administration of Levetiracetam concentrate for solution for infusion to achieve a total daily dose of 500 mg, 1,000 mg, 2,000 mg, or 3,000 mg in two divided doses.

**Table:** Preparation and administration of Levetiracetam concentrate for solution for infusion

Dose	Withdrawal Volume	Volume of Diluent	Infusion Time	Frequency of Administration	Total Daily Dose
250 mg	2.5 ml (half 5 ml vial)	100 ml	15 minutes	Twice daily	500 mg/day
500 mg	5 ml (one 5 ml vial)	100 ml	15 minutes	Twice daily	1000 mg/day

1000 mg	10 ml (two 5 ml vials)	100 ml	15 minutes	Twice daily	2000 mg/ day
1500 mg	15 ml (three 5 ml vials)	100 ml	15 minutes	Twice daily	3000 mg/ day

This medicinal product is for single use only, any unused solution should be discarded. Levetiracetam concentrate for solution for infusion was found to be chemically and physically stable and compatible when mixed with the following diluents for at least 24 hours and stored in PVC bags or PP bottles under controlled temperature of 25 °C.

**Diluents:**

- Sodium chloride 9 mg/ml (0.9%) solution for injection, USP
- Hartmann's or Ringer's lactate solution for injection
- Dextrose 50 mg/ml (5%) solution for injection, USP

Medicinal product with particulate matter or discoloration should not be used.

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

**7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES**

**Puniska Healthcare Pvt Limited,**

Survey No. 168/1/1, Pipan, Sanand,

Dist: Ahmedabad-382 110,

Gujarat, **INDIA.**

**8. MARKETING AUTHORIZATION NUMBER**

TAN 22 HM 0502

**9. DATE OF FIRST REGISTRATION / RENEWAL OF THE REGISTRATION**

05<sup>th</sup> December, 2022

**10. DATE OF REVISION OF THE TEXT**