FPO

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LEVETIRACETAM VIATRIS

Levetiracetam Concentrate for Solution for Infusion

100 mg/mL

NAME OF THE MEDICINAL PRODUCT:

Levetiracetam Concentrate for Solution for Infusion 100 mg/mL

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains: Levetiracetam 100 mg.

EXCIPIENTS

Sodium chloride
Sodium acetate
Glacial acetic acid
Water for injection
Nitrogen

PHARMACEUTICAL FORM:

Concentrate for Solution for Infusion.
A clear, colourless solution.

INDICATIONS

Levetiracetam 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.

Levetiracetam 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.
- myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.
- primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy.

Levetiracetam concentrate is an alternative for patients (adults and children from 4 years of age) when oral administration is temporarily not feasible.

DOSAGE AND 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.

Levetiracetam concentrate is for intravenous use only and the recommended dose must be diluted in at least 100 mL of a compatible diluent and a administered intravenously as 15-minute intravenous infusion (see Section **Incompatibilities and Use and Handling**). There is no experience with administration of intravenous levetiracetam for longer period than 4 days.

Levetiracetam concentrate is an alternative for patients (adults and children from 4 years of age) when oral administration is temporarily not feasible.

Route of Administration
For intravenous use:

Levetiracetam Concentrate for Solution for Infusion 100 mg/mL

Please refer to Section **Incompatibilities and Use and Handling** for recommendation on the preparation and administration of *Levetiracetam Concentrate for Solution for Infusion 100 mg/mL*.

Adults

- Monotherapy

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

- Add-on therapy

Adults (≥18 years) and adolescents (12 to 17 years) of 50 kg or more
The initial therapeutic dose is 500mg twice daily. This dose can be started on the first day of treatment.

Depending upon the clinical response and tolerance, the daily dose can be increased up to 1,500mg twice daily. Dose changes can be made in 500mg twice daily increases or decreases every two to four weeks.

Children

The physician should prescribe the most appropriate pharmaceutical form and strength according to age, weight and dose.

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

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

There are no data available.

Add-on Therapy for Children (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:

Weight	Starting dose: 10 mg/kg twice daily	Maximum dose: 30 mg/kg twice daily
15 kg [1]	150 mg (1.5 mL) twice daily	450 mg (4.5 mL) twice daily
20 kg [1]	200 mg (2 mL) twice daily	600 mg (6 mL) twice daily
25 kg	250 mg twice daily	750 mg twice daily
From 50 kg [2]	500 mg twice daily	1500 mg twice daily

[1] Children 25 kg or less should preferably start the treatment with Levetiracetam 100 mg/ml Oral Solution.

[2] Dosage in children and adolescents 50 kg or more is the same as in adults.

Infants and children less than 4 years
There are insufficient data to recommend the use of levetiracetam in children under 4 years of age.

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

Renal impairment
The daily dose must be individualised according to renal function (see section **Warnings and Precautions**). For adult patients, refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in mL/min is needed. The CLcr in mL/min may be estimated from serum creatinine(mg/dl) determination, for adults and adolescents weighing 50 kg or more, using the following formula:

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

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

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

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

Group	Creatinine clearance (mL/min/1.73m²)	Dosage and frequency
Normal	≥ 80	500 to 1,500mg 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 [1]	-	500 to 1,000mg 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.

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/1.73m² (see section **Warnings and Precautions**).

CONTRAINDICATIONS

Hypersensitivity to the active substance or other pyrrolidone derivatives or to any of the excipients.

WARNINGS AND PRECAUTIONS

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

An increase in seizure frequency of more than 25% has been reported in 14% of levetiracetam-treated adult and paediatric patients with partial onset seizures, whereas it was reported in 26% and 21% of placebo treated adult and paediatric patients, respectively.

When Levetiracetam was used to treat primary tonic-clonic seizures in adults and adolescents with idiopathic generalised epilepsy, there was no effect on the frequency of absences.

Renal or hepatic 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 **Dosage and Administration**).

Acute Kidney Injury
The use of Levetiracetam has been 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 (see Section **Adverse Reactions**).

Psychiatric Reactions
Behavioural abnormalities including psychotic symptoms, suicidal ideation, irritability and aggressive behaviour have been observed. Monitor patients for psychiatric signs and symptoms. If such behaviours are noticed, treatment adaptation or gradual discontinuation should be considered. If discontinuation is considered, please see Section *Discontinuation* in **Warnings and Precautions**.

A total of 13.3% of adult levetiracetam -treated patients and 37.6% of paediatric Levetiracetam -treated patients (4 to 16 years of age) compared to 6.2% and 18.6% of adult and paediatric placebo patients respectively, experienced non-psychotic behavioural symptoms (reported as aggression, a gitation, anger, anxiety, apathy, depersonalization, depression, emotional lability, hostility, hyperkinesias, irritability, nervousness, neurosis, and personality disorder).

A total of 1.7% of adult levetiracetam-treated patients discontinued treatment due to behavioural adverse events, compared to 0.2% of placebo patients. The treatment dose was reduced in 0.8% of adult levetiracetam-treated patients and in 0.5% of placebo patients. Overall, 10.9% of levetiracetam-treated paediatric patients experience behavioural symptoms associated with discontinuation or dose reduction, compared to 6.2% of placebo patients.

One percent of adult levetiracetam-treated patients experienced psychotic symptoms compared to 0.2% in the placebo patients.

Two (0.3%) adult levetiracetam-treated patients were hospitalized, and their treatment was discontinued due to psychosis. Both events, reported as psychosis, developed within the first week of treatment and resolved within 1 to 2 weeks following treatment discontinuation. There was no difference between drug and placebo-treated patients in the incidence of the paediatric patients who discontinued treatment due to psychotic and non-psychotic adverse reactions.

Depression and/or suicidal ideation
Suicide, suicide attempt and suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents (including levetiracetam). A meta-analysis of randomised 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.

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 preexisting cardiac disease or electrolyte disturbances.

Paediatric population
The tablet formulation is not adapted for use in 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.

Excipients
Solution for Infusion

This medicinal product contains 2.5 mmol (or 57 mg) sodium per maximum single dose (0.83 mmol (or 19 mg) per vial). It should be taken into consideration by patients on a controlled sodium diet.

DRUG INTERACTIONS

Anti-epileptic medicinal products
Pre-marketing data from clinical studies conducted in adults indicate that levetiracetam did not influence the serum concentrations of existing anti-epileptic medicinal products (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these anti-epileptic 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 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 anti-epileptic 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, digoxin and warfarin
Levetiracetam 1000mg daily did not influence the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel); endocrine parameters (luteinising hormone and progesterone) were not modified. Levetiracetam 2000mg 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.

PREGNANCY AND LACTATION

Fertility
No impact on fertility was detected in animal studies. No clinical data are available, potential risk for human is unknown.

Women of childbearing 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 anti-epileptic 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 anti-epileptic medicines AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated anti-epileptics.

Pregnancy
A large amount of post-marketing data on pregnant women exposed to levetiracetam monotherapy (more than 1800, among which in more than 1500 exposure occurred during the first 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. Studies in animals have shown reproductive toxicity.

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.

Lactation
Levetiracetam is excreted in human breast milk. Therefore, breast-feeding is not recommended. However, if levetiracetam treatment is needed during breast-feeding, the benefit/risk of the treatment should be weighed considering the importance of breast-feeding.

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, 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.

ADVERSE REACTIONS

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

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency.

Frequencies are defined as:

Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1000 to <1/100
Rare ≥1/10000 to <1/1000
Very rare <1/10000
Not known (cannot be estimated from the available data)

Infections and infestations
Very Common: nasopharyngitis
Rare: infection
Blood and lymphatic system disorders
Uncommon: thrombocytopenia, leukopenia
Rare: pancytopenia, neutropenia, agranulocytosis
Immune system disorders
Rare: drug reaction with eosinophilia and systemic symptoms (DRESS), hypersensitivity (including angioedema and anaphylaxis)
Metabolism and nutrition disorders
Common: anorexia
Uncommon: weight decreased, weight increase
Rare: hyponatraemia
Psychiatric disorders
Common: depression, hostility/aggression, anxiety, insomnia, nervousness/irritability
Uncommon: suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusional state, panic attack, affect lability/mood swings, agitation
Rare: completed suicide, personality disorder, thinking abnormal, delirium
Nervous system disorders
Very common: somnolence, headache
Common: convulsion, balance disorder, dizziness, lethargy, tremor

FRONT SIDE

ARTWORK DETAIL LABEL

PRODUCT	**LEVETIRACETAM VIATRIS – Levetiracetam Concentrate for Solution for Infusion 100 mg/mL**						
BUYER / COUNTRY	Mylan / Singapore						
DIMENSION	**400 x 260 mm**	COMPONENT	Pack Insert	PACK	NA	NO. OF COLOURS	1
COLOUR SHADES	Black						
VERSION & DATE	**Ver. 3; Date: 22.08.2023**						
SPECIAL INSTRUCTIONS	Dimensions may change during commercial supply.						

Uncommon: amnesia, memory impairment, coordination abnormal/ataxia, paraesthesia, disturbance in attention
Rare: choreoathetosis, dyskinesia, hyperkinesia, gait disturbance, encephalopathy, seizures aggravated
Eye disorders
Uncommon: diplopia, vision blurred
Ear and labyrinth disorders
Common: vertigo
Cardiac disorders
Rare: electrocardiogram QT prolonged
Respiratory, thoracic and mediastinal disorders
Common: cough
Gastrointestinal disorders
Common: abdominal pain, diarrhoea, dyspepsia, vomiting, nausea
Rare: pancreatitis
Hepatobiliary disorders
Uncommon: liver function test abnormal
Rare: hepatic failure, hepatitis
Renal and urinary disorders
Rare: acute kidney injury
Skin and subcutaneous tissue disorders
Common: rash
Uncommon: alopecia, eczema, pruritus
Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme
Musculoskeletal and connective tissue disorders
Uncommon: muscular weakness, myalgia
Rare: rhabdomyolysis and blood creatine phosphokinase increased*
General disorders and administration site conditions
Common: asthenia/fatigue
Injury, poisoning and procedural complications
Uncommon: injury
*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 co-administered with topiramate.

In several cases of alopecia, recovery was observed when Levetiracetam was discontinued.

Bone marrow suppression was identified in some of the cases of pancytopenia.

Cases of encephalopathy generally occurred at the beginning of the treatment (few days to a few months) and were reversible after treatment discontinuation.

Paediatric population

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 this paediatric age range, the data are supplemented with post-marketing experience of the use of Levetiracetam.

The adverse event 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.

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 regards 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.

OVERDOSAGE

Symptoms and signs

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

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group

Anti-epileptics, Other Anti-epileptics

ATC code

N03AX14.

Mechanism of action

The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing anti-epileptic active substances.

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^{2+} levels by partial inhibition of N-type Ca^{2+} currents and by reducing the release of Ca^{2+} from intraneuronal stores. In addition, it partially reverses the reductions in GABA- and glycine-gated currents induced by zinc and β-carbolines. Furthermore, levetiracetam has been shown in *in vitro* studies to bind to a specific site in rodent brain tissue. This binding site is the synaptic vesicle protein 2A, believed to be involved in vesicle fusion and neurotransmitter exocytosis. Levetiracetam and related analogs show a rank order of affinity for binding to the synaptic vesicle protein 2A which correlates with the potency of their anti-seizure protection in the mouse audiogenic model of epilepsy. This finding suggests that the interaction between levetiracetam and the synaptic vesicle protein 2A seems to contribute to the anti-epileptic mechanism of action of the medicinal product.

Pharmacodynamic effects

Levetiracetam induces seizure protection in a broad range of animal models of partial and primarily generalised seizures without having a pro-convulsant effect. The primary metabolite is inactive.

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

Pharmacokinetics

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.

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).

The pharmacokinetic profile has been characterised 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.

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 1000 mg dose and repeated 1000 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.

Peak plasma concentration (Cmax) 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).

Metabolism

Levetiracetam is not extensively metabolised in humans. The major metabolic pathway (24% of the dose) is an enzymatic hydrolysis of the acetamide group. Production of the primary metabolite, ucb L057, is not supported by liver cytochrome P450 isoforms. Hydrolysis of the acetamide group was measurable in a large number of tissues including blood cells. The metabolite ucb L057 is pharmacologically inactive.

Two minor metabolites were also identified. One was obtained by hydroxylation of the pyrrolidone ring (1.6% of the dose) and the other one by opening of the pyrrolidone ring (0.9% of the dose).

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 CYP1A1/2, 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±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.

Special patient populations

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 4-12 years after intravenous and oral administration.

Following single 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.

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 levetiracetam, based on creatinine clearance in patients with moderate and severe renal impairment.

In anuric end-stage renal disease 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 (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment, the pharmacokinetics of levetiracetam were unchanged. In subjects 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 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.

Gender

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

Race

Formal pharmacokinetic studies of the effects of race have not been conducted. Cross study comparisons involving Caucasians (N=12) and Asians (N=12), however, show that pharmacokinetics of levetiracetam were comparable between the two races. Because levetiracetam is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

INCOMPATIBILITIES AND USE AND HANDLING

Levetiracetam Concentrate for Solution for Infusion 100 mg/ml

Table presents the recommended preparation and administration of Levetiracetam concentrate to achieve a total daily dose of 500 mg, 1000 mg, 2000 mg or 3000 mg in two divided doses

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.

This medicinal product must not be mixed with other medicinal products except those mentioned below.

Levetiracetam concentrate for solution for infusion was found to be physically compatible and chemically stable for at least 24 hours when mixed with the following diluents and stored at room temperature (15-25°C), 2 to 8°C and 30°C.

Diluents:

- Sodium chloride 9 mg/mL (0.9%) solution for injection
- Lactated Ringer's solution for injection
- Dextrose 50 mg/mL (5%) solution for injection

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

STORAGE CONDITIONS

Store below 30°C.

SHELF LIFE

24 Months

Concentrate for solution for infusion: Refer to the storage condition on the outer packaging. From a microbiological point of view, the product should be used immediately after dilution. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C or at room temperature (15-25°C), unless dilution has taken place in controlled and validated aseptic conditions.

NATURE AND CONTENTSOF CONTAINER

Levetiracetam concentrate for solution for infusion 100 mg/mL: 5 mL/20 mm Tubular Fiolax Flint Type I flint vial with 20 mm rubber closures and 20 mm flip off aluminium seal.

DATE OF REVISION OF PACKAGE INSERT

August, 2023

For further information, please consult your physician or pharmacist.

NAME AND ADDRESS OF MANUFACTURER

Mylan

Mylan Laboratories Limited [HSF]
Plot No.14, Sipcot-II,
Krishnagiri Road, Hosur,
Tamil Nadu - 635 130, India.

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FPO

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BACK SIDE

ARTWORK DETAIL LABEL

PRODUCT	**LEVETIRACETAM VIATRIS – Levetiracetam Concentrate for Solution for Infusion 100 mg/mL**						
BUYER / COUNTRY	Mylan / Singapore						
DIMENSION	**400 x 260 mm**	COMPONENT	Pack Insert	PACK	NA	NO. OF COLOURS	1
COLOUR SHADES	Black						
VERSION & DATE	**Ver. 3; Date: 22.08.2023**						
SPECIAL INSTRUCTIONS	Dimensions may change during commercial supply.						