

Prescribing Information

For the use of Registered Medical Practitioner or Hospital or Laboratory Only.

Levetroy

Levetiracetam 100 mg/mL
Concentrate for Solution for Infusion

PRODUCT NAME:

LEVETROY (Levetiracetam 100 mg/ml concentrate for solution for infusion)

NAME AND STRENGTH OF ACTIVE SUBSTANCE(S):

Each ml contains 100 mg of levetiracetam

PRODUCT DESCRIPTION:

Clear, colorless to light yellow solution filled in 5 ml clear, colorless flint glass ampoule with blue OPC. Upon dilution with 0.9% sodium chloride, 5% Dextrose or Lactated Ringer's, it remains a clear, colorless solution.

PHARMACODYNAMICS/PHARMACOKINETICS:

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. 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.

Absorption: Levetiracetam is rapidly absorbed after oral administration. Oral absolute bioavailability is close to 100%.

Distribution: 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 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±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.

Children (4 to 12 years): Following single oral dose administration (20 mg/kg) to epileptic children (6 to 12 years), the half-life of levetiracetam was 6.0 hours. The apparent body weight adjusted clearance was approximately 30% higher than in epileptic adults.

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

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 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.

Pharmacodynamics

Pharmacotherapeutic group: Antiepileptics; Other Antiepileptics

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 antiepileptic 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 Ca²⁺ levels by partial inhibition of N-type Ca²⁺ currents and by reducing the release of Ca²⁺ from intraneuronal stores. In addition it partially reverses the reductions in GABA- and glycine-gated currents induced by zinc and β-carbolines. Furthermore, levetiracetam has been shown in in vitro studies to bind to a specific site in rodent brain tissue. This binding site is the synaptic vesicle protein 2A, believed to be involved in vesicle fusion and neurotransmitter exocytosis. Levetiracetam and related analogs show a rank order of affinity for binding to the synaptic vesicle protein 2A which correlates with the potency of their anti-seizure protection in the mouse audiogenic model of epilepsy. This finding suggests that the interaction between levetiracetam and the synaptic vesicle protein 2A seems to contribute to the antiepileptic mechanism of action of the medicinal product.

Pharmacodynamic effect: 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/photoparoxysmal response) has confirmed the broad spectrum pharmacological profile of levetiracetam.

INDICATION:

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

Levetroy is indicated as adjunctive therapy:

- in the treatment of partial onset seizures with or without secondary generalisation in adults 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 children 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.

RECOMMENDED DOSAGE:

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 diluents and administered intravenously as a 15-minute intravenous infusion. 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.

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) 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 1500 mg twice daily. Dose changes can be made in 500 mg twice daily increases or decreases every two to four weeks.

Children

The physician should prescribe the most appropriate pharmaceutical form, presentation and strength according to age, weight and dose. The safety and efficacy of levetiracetam concentrate for solution for infusion in infants and 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

- 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 for all indications. 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
10 kg ⁽¹⁾	100 mg (1 ml) twice daily	300 mg (3 ml) 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⁾ Dose in children and adolescents 50 kg or more is the same as in adults

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.

For adult patients, refer to the following table and adjust the dose as indicated. To use this dosing table, an

estimate of the patient's creatinine clearance (CLcr) in ml/min is needed.

The CLcr in ml/min may be estimated from serum creatinine (mg/dl) determination, for adults and adolescents weighting 50 kg or more, using 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 adolescent patients weighing more than 50kg with impaired renal function

Group	Creatinine clearance ml/min/1.73m ²	Dosage and frequency
Normal	≥ 80	500 to 1500 mg twice daily
Mild	50-79	500 to 1000 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 1000 mg once daily ⁽²⁾

⁽¹⁾ A 750 mg loading dose is recommended on the first day of treatment with levetiracetam.

⁽²⁾ Following dialysis, a 250 to 500 mg supplemental dose is recommended.

For children with renal impairment, levetiracetam dose needs to be adjusted based on the renal function as levetiracetam clearance is related to renal function.

This recommendation is based on a study in adult renally impaired patients.

The CLcr in ml/min/1.73 m² may be estimated from serum creatinine (mg/dl) determination using, 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.

Group	Creatinine clearance (ml/min/1.73m ²)	Children and adolescents weighing less than 50 kg
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 ⁽²⁾⁽³⁾

⁽²⁾ A 15 mg/kg (0.15 ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.

⁽³⁾ 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/1.73m².

ROUTE OF ADMINISTRATION:

For intravenous use.

CONTRAINDICATIONS:

Levetiracetam is contraindicated in:

- 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 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).

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.

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.

Depression and/or suicidal ideation

Potential for an increase in risk of suicidal thoughts or behaviors.

Suicide, suicide attempt, suicidal ideation and behaviour have been reported in patients treated with anti-

epileptic agents (including levetiracetam). A meta-analysis of randomized placebo-controlled trials of anti-epileptic medicinal products has shown a small increased risk of suicidal thoughts and behaviour. The mechanism of this risk is not known.

Therefore patients should be monitored for signs of depression and/or suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of depression and/or suicidal ideation or behaviour emerge.

Abnormal and aggressive behaviours

Levetiracetam may cause psychotic symptoms and behavioural abnormalities including irritability and aggressiveness. Patients treated with levetiracetam should be monitored for developing psychiatric signs suggesting important mood and/or personality changes.

If such behaviours are noticed, treatment adaptation or gradual discontinuation should be considered. If discontinuation is considered please see *Discontinuation*

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 Sodium chloride, Sodium acetate and Glacial acetic acid.

It should be taken into consideration by patients on a controlled sodium diet.

INTERACTIONS WITH OTHER MEDICAMENTS:

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.

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. Dosage 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 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 2000 mg daily did not influence the pharmacokinetics of digoxin and warfarin; prothrombin times were not modified. Co-administration with digoxin, oral contraceptives and warfarin did not influence the pharmacokinetics of levetiracetam.

Laxatives

There have been isolated reports of decreased levetiracetam efficacy when the osmotic laxative macrogol has been concomitantly administered with oral levetiracetam. Therefore, macrogol should not be taken orally for one hour before and for one hour after taking levetiracetam.

Food and alcohol

The extent of absorption of levetiracetam was not altered by food, but the rate of absorption was slightly reduced. No data on the interaction of levetiracetam with alcohol are available.

STATEMENT ON USAGE DURING PREGNANCY AND LACTATION:

Pregnancy: A large amount of postmarketing 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.

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 breastfeeding, the benefit/risk of the treatment should be weighed considering the importance of breastfeeding.

ABILITY TO PERFORM TASKS THAT REQUIRE JUDGEMENT, MOTOR OR COGNITIVE SKILLS:

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.

ADVERSE EFFECTS/ UNDESIRABLE EFFECTS:

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: neutropenia, pancytopenia, 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

Uncommon: amnesia, memory impairment, coordination abnormal/ataxia, paraesthesia, disturbance in attention

Rare: choreoathetosis, dyskinesia, hyperkinesia, gait disturbance, encephalopathy

Eye disorders

Uncommon: diplopia, vision blurred

Ear and labyrinth disorders

Common: vertigo

Respiratory, thoracic and mediastinal disorders

Common: cough

Gastrointestinal disorders

Common: abdominal pain, diarrhoea, dyspepsia, nausea, vomiting

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 have been rarely observed after levetiracetam administration. These undesirable effects are generally occurred at the beginning of the treatment (few days to a few months) and were reversible after treatment discontinuation.

OVERDOSE AND TREATMENT:

Symptoms and signs:

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

Treatment:

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.

INSTRUCTIONS FOR USE:

Levetiracetam 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.

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.

Table presents the recommended preparation and administration of levetiracetam concentrate to achieve a total daily dose of 500 mg, 1,000 mg, 2,000 mg, or 3,000 mg in two divided doses.

Dose	Withdrawal Volume	Volume of Diluent	Infusion time	Frequency of administration	Total Daily Dose
250 mg	2.5 ml	100 ml	15 minutes	Twice daily	500 mg/day
500 mg	5 ml	100 ml	15 minutes	Twice daily	1000 mg/day
1000 mg	10 ml	100 ml	15 minutes	Twice daily	2000 mg/day
1500 mg	15 ml	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 was found to be physically compatible and chemically stable when mixed with the following diluents for at least 24 hours and stored in PVC bags at controlled room temperature 15- 25°C and 2- 8°C.

Diluents:

- Sodium chloride (0.9%) injection
- Lactated Ringer's injection
- Dextrose 5% injection

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

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

SHELF LIFE AND STORAGE CONDITION:

Unopened: 36 months. Store below 30°C. Protect from light.

Upon dilution: Levetiracetam 100mg/mL concentrate for solution for infusion was found to be physically compatible and chemically stable up to 24 hours when mixed with a suitable diluent and stored in PVC bags at controlled room temperature 15-25°C and 2-8 °C.

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

DOSAGE FORMS AND PACKAGING AVAILABLE:

Solution for Infusion in colorless glass 5 ml flint ampoule with blue OPC (Ph.Eur. Type-I).

REGISTRATION HOLDER AND IMPORTER:

Unimed Sdn. Bhd,
53, Jalan Tembaga SD 5/2B,
Bandar Sri Damansara, 52200
Kuala Lumpur, Malaysia

DATE OF REVISION OF PI:

04/06/2024

Manufactured by:



Troikaa Pharmaceuticals Ltd.

C-1, Sara Industrial Estate, Selaqui, Dehradun, Uttarakhand, India

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