



Asu Levetiracetam Concentrate Solution for Infusion 100mg/ml

COMPOSITION

ACTIVE INGREDIENT	
Levetiracetam	100mg/ml
EXCIPIENTS	
Sodium Chloride	9mg /ml
Sodium Acetate Trihydrate	1.64mg/ml
Glacial Acetic Acid	q.s
Water for injection	q.s to 5 ml

PRODUCT DESCRIPTION

Asu Levetiracetam Concentrate Solution for Infusion 100mg/ml contains levetiracetam as active ingredients. It is clear and colorless solution which free from readily visible particles. Levetiracetam injection is supplied in 5ml clear glass vials. Each vial contains 5ml of levetiracetam injection.

The Levetiracetam injection is an antiepileptic drug available as a clear, colorless, sterile solution (100 mg/mL) for intravenous administration. The Levetiracetam injection is for intravenous use only and should be diluted in 100 mL of a compatible diluent prior to administration. The diluted solution should be clear colorless.

PHARMACODYNAMICS

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.

Pharmacodynamic effects

Levetiracetam induces seizure protection in a broad range of animal models of partial and primary generalized seizures without having a pro-convulsant effect. The primary metabolite is inactive. In man, an activity in both partial and generalized 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. There is no evidence for any relevant gender,

race or circadian variability. 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.

Absorption

Levetiracetam is rapidly absorbed after oral administration. Oral absolute bioavailability is close to 100 %. Peak plasma concentrations (C_{max}) are achieved at 1.3 hours after dosing. Steady-state is achieved after two days of a twice daily administration schedule. 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.

Metabolism

Levetiracetam is not extensively metabolise 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.

INDICATION

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

Levetiracetam is indicated as adjunctive therapy in the treatment of:

- Partial onset seizures with or without secondary generalization in adults, children and infants from 4 years of age with epilepsy.
- Myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.
- Primary generalized tonic-clonic seizures in adults and adolescents from 16 years of age with Idiopathic Generalized 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.

Concentrate for solution for infusion

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 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.

ROUTE OF ADMINISTRATION

Intravenous

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Discontinuation

In accordance with current clinical practice, if Levetiracetam has to be discontinued it is recommended to withdraw it gradually (e.g. in adults and adolescents weighing more than 50 kg or more: reduce dose by 500 mg twice daily every two to four weeks; in 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.

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 count (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

Suicide, suicide attempt, suicidal ideation and behavior have been reported in patients treated with anti-epileptic agents (including levetiracetam). It has potential for an increase in risk of suicidal thoughts or behavior. A meta-analysis of randomized placebo-controlled trials of anti-epileptic medicinal products has shown a small increased risk of suicidal thoughts and behavior. The mechanism of this risk is not known. Therefore patients should be monitored for signs of depression and/or suicidal ideation and behaviors 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 behavior emerge.

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.

Sodium content precaution

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.

Antiepileptic medicinal products

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. The adjunctive therapy with orally administered levetiracetam did not influence the steady-state serum concentrations of concomitantly administered carbamazepine and valproate. However, 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, 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 2,000 mg daily did not influence the pharmacokinetics of digoxin and warfarin; prothrombin times were not modified. Coadministration 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

Pregnancy

Levetiracetam is not recommended during pregnancy and in women of childbearing potential not using contraception unless clearly necessary. Therapy with multiple antiepileptic medicinal products is associated with a higher risk of congenital malformations than monotherapy and, therefore, monotherapy should be considered.

Physiological changes during pregnancy may affect levetiracetam concentration. Appropriate clinical management of pregnant women treated with levetiracetam should be ensured. Discontinuation of antiepileptic treatments may result in exacerbation of the disease which could be harmful to the mother and the fetus.

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.

ADVERSE EFFECTS

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: hyponatremia

Psychiatric disorders

Common: depression, hostility/aggression, anxiety, insomnia, nervousness/irritability

Uncommon: suicide attempt, suicidal ideation, psychotic disorder, abnormal behavior, hallucination, anger, confusional state, panic attack, affect lability/mood swings, agitation

Rare: completed suicide, personality disorder, thinking abnormal

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

Eye disorders

Uncommon: diplopia, vision blurred

Ear and labyrinth disorders

Common: vertigo

Respiratory, thoracic and mediastinal disorders

Common: cough

Gastrointestinal disorders

Common: abdominal pain, diarrhea, 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, Steven s-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.

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 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.



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 hemodialysis. The dialyzer 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 center, where available.

EFFECTS ON ABILITY TO USE AND DRIVE MACHINE

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.

INSTRUCTION FOR USE

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 not more than 4 hours and stored in PVC bags at controlled room temperature 15-30°C.

Diluents:

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

Each 5ml of levetiracetam concentrate vial contains 500mg Levetiracetam. 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
250mg	2.5 ml (half 5ml vial)	100 ml	15 minutes	Twice daily	500 mg/day
500mg	5ml (one 5ml vial)	100 ml	15 minutes	Twice daily	1000 mg/day
1000mg	10 ml (two 5ml vials)	100 ml	15 minutes	Twice daily	2000 mg/day
1500mg	15 ml (three 5ml vials)	100 ml	15 minutes	Twice daily	3000 mg/day

INCOMPATIBILITIES OF PRODUCT

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1500mg	15 ml (three 5ml 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 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.

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.

STORAGE CONDITIONS

Unopened vial:

Store below 30°C

After dilution:

It should be used immediately after dilution

PACKAGING

Asu Levetiracetam Concentrate Solution for Infusion 100mg/ml in 5ml type I clear glass vial, seal with 13mm V-55/4432 rubber stopper (made of chlorobutyl) and overseal with 13mm blue flip-off aluminum seal. 10 vials was packed in one printed box.

MANUFACTURER

UBI Pharma Inc.

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PRODUCT REGISTRATION HOLDER

Asumed Biotech Sdn. Bhd.

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Selangor.

MALAYSIA REGISTRATION NUMBER

MALXXXXX

REVISION DATE

27/10/2022

ATC CODE

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