

SUMMARY OF PRODUCT CHARACTERISTICS(SPC)

1. NAME OF THE MEDICINAL PRODUCT

Kepam 500mg/5ml solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Vial contains

Levetiracetam.....500mg

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

KEPAM® injection is an alternative for adult patients (16 years and older) when oral administration is temporarily not feasible.

Partial Onset Seizures: KEPAM® is indicated as adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy.

Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy: KEPAM® is indicated as adjunctive therapy in the treatment of myoclonic seizures in adults with juvenile myoclonic epilepsy.

Primary Generalized Tonic-Clonic Seizures; KEPAM® is indicated as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults with idiopathic generalized epilepsy.

4.2 Posology and method of administration

General Information:

KEPAM® injection is for intravenous use only and must be diluted prior to administration. **KEPAM®** injection (500 mg/5 ml) should be diluted in 100 ml of a compatible diluent and administered intravenously as a 15-minute IV infusion.

Product with particulate matter or discoloration should not be used.

Any unused portion of the KEPAM injection vial contents should be discarded.

Initial Exposure to levetiracetam:

Levetiracetam can be initiated with either intravenous or oral administration.

Partial Onset Seizures

for oral levetiracetam, daily doses of 1000 mg, 2000 mg, and 3000 mg, given as twice-daily dosing, shown to be effective. a consistent increase in response with increased dose has not been shown. Treatment should be initiated with a daily dose of 1000 mg/day, given as twice-daily dosing (500 mg twice daily). Additional dosing increments may be given (1000 mg/day additional every 2 weeks) to a maximum recommended daily dose of 3000 mg. There is no evidence that doses greater than 3000 mg/day confer additional benefit.

Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy

Treatment should be initiated with a dose of 1000 mg/day, given as twice-daily dosing (500 mg twice daily). Dosage should be increased by 1000 mg/day every 2 weeks to the recommended daily dose of 3000 mg. The effectiveness of doses lower than 3000 mg/day has not been studied.

Primary Generalized Tonic-Clonic Seizures

Treatment should be initiated with a dose of 1000 mg/day, given as twice-daily dosing (500 mg BID). Dosage should be increased by 1000 mg/day every 2 weeks to the recommended daily dose of 3000 mg. The effectiveness of doses lower than 3000 mg/day has not been adequately studied.

Replacement Therapy:

When switching from oral Levetiracetam, the initial total daily intravenous dosage of **KEPAM**[®] should be equivalent to the total daily dosage and frequency of oral levetiracetam and should be administered as a 15-minute intravenous infusion following dilution in 100 ml of a compatible diluent.

Switching to Oral Dosing:

At the end of the intravenous treatment period, the patient may be switched to Levetiracetam oral administration at the equivalent daily dosage and frequency of the intravenous administration.

Dosing Instructions:

KEPAM[®] injection is for intravenous use only and must be diluted prior to administration. One vial of **KEPAM**[®] injection contains 500 mg levetiracetam (500 mg/5 ml). See Table 1 for the recommended preparation and administration of **KEPAM**[®] injection to achieve a dose of 500 mg, 1000 mg, or 1500 mg.

Table I: Preparation and Administration of KEPAM Injection

Dose	Withdraw Volume	Volume of Diluent	Infusion Time
500mg	5 mL (5 ml vial)	100ml	15 minutes
1000mg	10 mL (two 5 ml vials)	100ml	15 minutes
1500mg	15 mL (three 5 ml vials)	100ml	15 minutes

For example, to prepare a 1000 mg dose, dilute 10 mL of **KEPAM**[®] injection in 100 mL of a compatible diluent and administer intravenously as a 15-minute infusion.

Adult Patients with Impaired Renal Function:

KEPAM[®] dosing must be individualized according to the patient's renal function status. Recommended doses and adjustment for dose for adults are shown in Table 2, in order to calculate the dose recommended for patients with renal impairment, creatinine clearance adjusted for body surface area must be calculated. To do this an estimate of the patient's creatinine clearance (CL_{cr}) in mL/min must first be calculated using the following formula:

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

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

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

Table 2: Dosing Adjustment Regimen for Adult Patients with Impaired Renal Function

Group	Creatinine Clearance (ml/min/1.73m ²)	Dosage (mg)	Frequency Normal
Normal	>80	500 to 1,500	Every 12 hours
Mild	50—80	500 to 1,000	Every 12 hours
Moderate	30—50	250 to 750	Every 12 hours
Severe	<30	250 to 500	Every 12 hours
ESRD patients using dialysis	-----	500 to 1,000	Every 24 hours

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

Compatibility and Stability

KEPAM® injection was found to be physically compatible and chemically stable when mixed with the following diluents for at least 24 hours and stored in polyvinyl chloride (PVC) bags at controlled room temperature not more than 30°C.

Diluents

- Sodium chloride (0.9%)
- Glucose 5%

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

4.3 Contraindications

NA.

4.4 Special warnings and precautions for use

Psychiatric Reactions:

In some patients levetiracetam causes behavioral abnormalities.

Some Reports regarding using levetiracetam, Patients experienced non-psychotic behavioral symptoms (aggression, agitation, anger, anxiety, apathy, depersonalization, depression, emotional lability, hostility, irritability, and nervousness).

These events, reported as psychosis, developed within the first week of treatment and resolved within 1 to 2 weeks following treatment discontinuation.

The above psychiatric signs and symptoms should be monitored.

Somnolence and Fatigue:

In some patients, levetiracetam causes somnolence and fatigue.

Somnolence and asthenia occurred most frequently within the first 4 weeks of treatment. Patients should be monitored for these signs and symptoms and advised not to drive or operate machinery until they have gained sufficient experience on **KEPAM®** to gauge whether it adversely affects their ability to drive or operate machinery.

Serious Dermatological reactions:

Serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in patients treated with levetiracetam. The median time of onset is reported to be 14 to 17 days, but cases have been reported at least four months after initiation of treatment. Recurrence of the serious skin reactions following rechallenge with levetiracetam has also been reported. levetiracetam should be discontinued at the first sign of a rash, unless the rash is clearly not drugrelated. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered.

Coordination Difficulties:

Coordination difficulties were only observed in the adult partial onset seizure. Adult levetiracetam-treated patients experienced coordination difficulties, (reported as either ataxia, abnormal gait, or incoordination).

These events occurred most frequently within the first 4 weeks of treatment.

Patients should be monitored for these signs and symptoms and advised not to drive or operate machinery until they have gained sufficient experience on **KEPAM®** to gauge whether it could adversely affect their ability to drive or operate machinery.

Withdrawal Seizures:

Antiepileptic drugs, including **KEPAM®**, should be withdrawn gradually to minimize the potential of increased seizure frequency.

Hematologic Abnormalities:

Partial Onset Seizures: Minor, but statistically significant.

Juvenile Myoclonic Epilepsy: Although there were no obvious hematologic abnormalities observed in patients with JME, limited data makes any conclusion tentative. The data from the partial seizure patients should be considered to be relevant for JME patients.

Seizure Control during Pregnancy:

Physiological changes may gradually decrease plasma levels of levetiracetam throughout pregnancy. This decrease is more pronounced during the third trimester. It is recommended that patients be monitored carefully during pregnancy. Close monitoring should continue through the postpartum period especially if the dose was changed during pregnancy.

Suicidal Behavior and Ideation

Counsel patients, their caregivers, and/or families that antiepileptic drugs (AEDs), including **Kepam®**, may increase the risk of suicidal thoughts and behavior and advise patients to be alert for the emergence or worsening of symptoms of depression; unusual changes in mood or behavior; or suicidal thoughts, behavior, or thoughts about self-harm. Advise patients, their caregivers, and/or families to immediately report behaviors of concern to a healthcare provider.

Psychiatric Reactions and Changes in Behavior

Advise patients that Levetiracetam may cause changes in behavior (e.g. aggression, agitation, anger, anxiety, apathy, depression, hostility, and irritability) and in rare cases, psychotic symptoms have occurred.

Pediatric Use

Safety and effectiveness of Levetiracetam injection in patients below the age of 16 years have not been established.

Geriatric Use

There were insufficient data to assess the effectiveness of Levetiracetam in these patients. Levetiracetam is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Use in Patients with Impaired Renal Function

Clearance of levetiracetam is decreased in patients with renal impairment and is correlated with creatinine clearance [see Clinical Pharmacology (12.3)]. Dosage adjustment is recommended for patients with impaired renal function and supplemental doses should be given to patients after dialysis.

4.5 Interaction with other medicinal products and other forms of interaction

No significant pharmacokinetic interactions were observed between levetiracetam or its major metabolite and concomitant medications via human liver cytochrome P450 isoforms, epoxide hydrolase, UDP-glucuronidation enzymes, P-glycoprotein, or renal tubular secretion.

Phenytoin: levetiracetam (3000 mg daily) had no effect on the pharmacokinetic disposition of phenytoin in patients with refractory epilepsy.

Pharmacokinetics of levetiracetam was also not affected by phenytoin.

Valproate: levetiracetam (1500 mg twice daily) did not alter the pharmacokinetics of valproate. Valproate 500 mg twice daily did not modify the rate or extent of levetiracetam absorption or its plasma clearance or urinary excretion. There also was no effect on exposure to and the excretion of the primary metabolite.

Other Antiepileptic Drugs: Potential drug interactions between levetiracetam and other AEDs (carbamazepine, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone and valproate) levetiracetam does not influence the plasma concentration of other AEDs and that these AEDs do not influence the pharmacokinetics of levetiracetam.

Oral Contraceptives: levetiracetam (500 mg twice daily) did not influence the pharmacokinetics of an oral contraceptive containing 0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel, or of the luteinizing hormone and progesterone levels, indicating that impairment of contraceptive efficacy is unlikely. Co-administration of this oral contraceptive did not influence the pharmacokinetics of levetiracetam.

Digoxin: levetiracetam (1000 mg twice daily) did not influence the pharmacokinetics and pharmacodynamics (ECO) of digoxin given as a 0.25 mg dose every day. Co-administration of digoxin did not influence the pharmacokinetics of levetiracetam.

Warfarin: levetiracetam (1000 mg twice daily) did not influence the pharmacokinetics of R and S warfarin. Prothrombin time was not affected by levetiracetam. Co-administration of warfarin did not affect the pharmacokinetics of levetiracetam.

Probenecid: Probenecid, a renal tubular secretion blocking agent, administered at a dose of 500 mg four times a day, did not change the pharmacokinetics of levetiracetam 1000 mg twice daily. C_{max} of the metabolite approximately doubled in the presence of probenecid while the fraction of drug excreted unchanged in the urine remain the same. Renal clearance of metabolite in the presence of probenecid will decrease for about 60%, probably related to competitive inhibition of tubular secretion of metabolite. The effect of levetiracetam on probenecid was not studied.

4.6 Pregnancy and lactation

Pregnancy:

levetiracetam levels may decrease during pregnancy.

Pregnancy C:

There are no adequate and well-controlled studies in pregnant women. In animal studies, levetiracetam produced evidence of developmental toxicity, including teratogenic effects, at doses similar to or greater than human therapeutic doses. **KEPAM®** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery:

The effect of levetiracetam on labor and delivery in humans is unknown.

Lactation:

Levetiracetam is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from levetiracetam, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

Inform patients that **KEPAM®** may cause dizziness and somnolence. Inform patients not to drive or operate machinery until they have gained sufficient experience on **KEPAM®** to gauge whether it adversely affects their ability to drive or operate machinery.

4.8 Undesirable effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The most frequently reported adverse reactions were nasopharyngitis, somnolence (sleepiness), headache, fatigue and dizziness. At the beginning of the treatment or at dose increase side effects like sleepiness, tiredness and dizziness may be more common. These effects should however decrease over time.

Very common: may affect more than 1 user in 10 people :

- nasopharyngitis;
- somnolence (sleepiness), headache.

Common: may affect 1 to 10 users in 100 people :

- anorexia (loss of appetite);
- depression, hostility or aggression, anxiety, insomnia, nervousness or irritability;
- convulsion, balance disorder (equilibrium disorder), dizziness (sensation of unsteadiness), lethargy (lack of energy and enthusiasm), tremor (involuntary trembling);
- vertigo (sensation of rotation);
- cough;
- abdominal pain, diarrhoea, dyspepsia (indigestion), vomiting, nausea;
- rash;
- asthenia/fatigue (tiredness).

Uncommon: may affect 1 to 10 users in 1000 people:

- decreased number of blood platelets, decreased number of white blood cells;
- weight decrease, weight increase;
- suicide attempt and suicidal ideation, mental disorder, abnormal behaviour, hallucination, anger, confusion, panic attack, emotional instability/mood swings, agitation; amnesia (loss of memory), memory impairment (forgetfulness), abnormal coordination/ataxia (impaired coordinated movements), paraesthesia (tingling), disturbance in attention (loss of concentration);
- diplopia (double vision), vision blurred;
- elevated/abnormal values in a liver function test;
- hair loss, eczema, pruritus;
- muscle weakness, myalgia (muscle pain); injury.

Rare: may affect 1 to 10 users in 10,000 people

- infection;
- decreased number of all blood cell types;
- severe allergic reactions (DRESS, anaphylactic reaction [severe and important allergic reaction], Quincke's oedema [swelling of the face, lips, tongue and throat]);
- decreased blood sodium concentration;
- suicide, personality disorders (behavioural problems), thinking abnormal (slow thinking, unable to concentrate);
- uncontrollable muscle spasms affecting the head, torso and limbs, difficulty in controlling movements, hyperkinesia (hyperactivity);
- pancreatitis;
- liver failure, hepatitis;
- skin rash, which may form blisters and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) (erythema multiforme), a widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome), and a more severe form causing skin peeling in more than 30% of the body surface (toxic epidermal necrolysis).

Dermatological Adverse Reactions

Advise patients that serious dermatological adverse reactions have occurred in patients treated with Levetiracetam and instruct them to call their physician immediately if a rash develops.

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 the National Regulatory Authority via Pharmacovigilance Electronic Reporting System (PvERS)

<https://pv.pharmacyboardkenya.org/>

4.9 Overdose

Signs, Symptoms and Laboratory Findings:

The highest known dose of oral levetiracetam was 6000 mg/day. Other than drowsiness, there were no adverse reactions in the few known cases of overdose. Cases of somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with levetiracetam overdoses in post marketing use.

Management of Overdose:

There is no specific antidote for overdose with levetiracetam. If indicated, elimination of unabsorbed drug should be attempted by emesis or gastric lavage; usual precautions should be observed to maintain airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the patient's clinical status.

Hemodialysis:

Standard hemodialysis procedures result in significant clearance of levetiracetam (approximately 50% in 4 hours) and should be considered in cases of overdose. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

5. Pharmacological properties

5.1 Pharmacodynamic properties

ATC code : N03AX14.

Mechanism of action

Pharmacotherapeutic group: antiepileptics, other antiepileptics.

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.

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^{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 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/photoparoxysmal 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 diluents 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_{max}) observed in 17 subjects following a single intravenous dose of 1500 mg infused over 15 minutes was 51 ± 19 µg/ml (arithmetic average $\pm$ 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 ± 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, 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 (see section 4.2).

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/m² 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/m² 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/m² 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/m² 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/m² basis)

6. Pharmaceutical particulars

6.1 List of excipients

Sodium acetate trihydrate

Sodium chloride

Glacial acetic acid

Water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Vial 6R with Rubber Stopper 20mm.

6.6 Special precautions for disposal and other handling

N.A.

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING ADDRESS

MS Pharma – Jordan

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8. MARKETING AUTHORIZATION NUMBER

H2019/CTD6901/13389/R1

9. DATE OF FIRST AUTHORIZATION /RENEWAL OF THE AUTHORIZATION

2025 September 19

10. DATE OF REVISION

2025 September 19