

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Levetiracetam in 0.82% Sodium Chloride Injection (500 mg/100ml),
EPIEND

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 ml contains Levetiracetam USP. 500 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Intravenous Infusion

4. CLINICAL PARTICULARS

4.1 Therapeutic

indications Partial-

Onset Seizures

Levetiracetam in Sodium Chloride Injection is indicated as adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy.

Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy

Levetiracetam in Sodium Chloride Injection is indicated as adjunctive therapy in the treatment of myoclonic seizures in adults with juvenile myoclonic epilepsy.

Primary Generalized Tonic-Clonic Seizures

Levetiracetam in Sodium Chloride Injection is indicated as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults with idiopathic generalized epilepsy.

Limitations of Use

Levetiracetam in Sodium Chloride Injection is an antiepileptic drug indicated for adult patients (16 years and older) when oral administration is temporarily not feasible.

4.2 Posology and method of

administration General

Information – Administration

Levetiracetam in Sodium Chloride Injection is for intravenous use only. A single-dose

100 mL bag should be administered intravenously over a 15-minute IV infusion period.

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

Levetiracetam in Sodium Chloride Injection should not be further diluted prior to use. Any unused portion of the Levetiracetam in Sodium Chloride Injection contents should be discarded.

Initial Exposure to Levetiracetam

Levetiracetam can be initiated with either intravenous or oral administration.

Partial-Onset Seizures

In clinical trials of oral levetiracetam, daily doses of 1000 mg, 2000 mg, and 3000 mg, given as twice-daily dosing, were shown to be effective. Although in some studies there was a tendency toward greater response with higher dose, 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. Doses greater than 3000 mg/day have been used in open-label studies with levetiracetam tablets for periods of 6 months and longer. 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 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 adequately studied.

Switching to Intravenous Dosing

When switching from oral levetiracetam, the initial total daily intravenous dosage of levetiracetam should be equivalent to the total daily dosage and frequency of oral levetiracetam.

Adult Patients with Impaired Renal Function

Levetiracetam dosing must be individualized according to the patient's renal function status. Recommended doses and adjustment for dose for adults are shown in Table 1. To use this dosing table, an estimate of the patient's creatinine clearance (CL_{cr}) in mL/min is needed.

Table 1: Dosing Adjustment Regimen for Adult Patients with Impaired Renal Function

Group	Creatinine Clearance (mL/min)	Dosage (mg)	Frequency
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.

For doses (e.g. 250 mg and 750 mg) not achievable with the available product strengths, using aseptic technique, withdraw the appropriate dose (see Table 1) from an intact commercial bag and place the measured dose in a separate empty, sterile infusion bag. Administer the prepared dose by intravenous infusion over a period of 15 minutes. The unused portion of the original commercial bag must be discarded. Do not store or reuse.

Discontinuation of Levetiracetam

Avoid abrupt withdrawal from levetiracetam in order to reduce the risk of increased seizure frequency and status epilepticus (see section 4.4).

4.3 Contraindications

Levetiracetam in Sodium Chloride Injection is contraindicated in patients with a hypersensitivity to levetiracetam or to any of the excipients listed in section 6.1. Reactions have included anaphylaxis and angioedema (see section 4.4).

4.4 Special warnings and precautions

for use Psychiatric Reactions

In some patients levetiracetam causes behavioral abnormalities. The incidences of behavioral abnormalities in the myoclonic and primary generalized tonic-clonic seizure studies were comparable to those of the adult partial-onset seizure studies.

A total of 13.3% of adult levetiracetam-treated patients compared to 6.2% of placebo patients experienced non-psychotic behavioral symptoms (reported as aggression, agitation, anger, anxiety, apathy, depersonalization, depression, emotional lability, hostility, irritability, and nervousness).

A total of 1.7% of adult levetiracetam-treated patients discontinued treatment due to behavioral 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.

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

The above psychiatric signs and symptoms should be monitored.

Somnolence and Fatigue

In some patients, levetiracetam causes somnolence and fatigue. The incidences of somnolence and fatigue provided below are from controlled adult partial-onset seizure studies. In general, the incidences of somnolence and fatigue in the myoclonic and primary generalized tonic-clonic studies were comparable to those of the adult partial onset seizure studies.

In controlled trials of adult patients with epilepsy experiencing partial-onset seizures, 14.8% of levetiracetam-treated patients reported somnolence, compared to 8.4% of placebo patients. There was no clear dose response up to 3000 mg/day. In a study where there was no titration, about 45% of patients receiving 4000 mg/day reported somnolence. The somnolence was considered serious in 0.3% of the treated patients, compared to 0% in the placebo group. About 3% of levetiracetam-treated patients discontinued treatment due to somnolence, compared to 0.7% of placebo patients. In 1.4% of treated patients and in 0.9% of placebo patients the dose was reduced, while 0.3% of the treated patients were hospitalized due to somnolence.

In controlled trials of adult patients with epilepsy experiencing partial-onset seizures, 14.7% of levetiracetam-treated patients reported asthenia, compared to 9.1% of placebo patients. Treatment was discontinued due to asthenia in 0.8% of treated patients as compared to 0.5% of placebo patients. In 0.5% of treated patients and in 0.2% of placebo patients the dose was reduced due to asthenia.

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 levetiracetam to gauge whether it adversely affects their ability to drive or operate machinery.

Anaphylaxis and Angioedema

Levetiracetam can cause anaphylaxis or angioedema after the first dose or at any time during treatment. Signs and symptoms in cases reported in the postmarketing setting with levetiracetam have included hypotension, hives, rash, respiratory distress, and swelling of the face, lip, mouth, eye, tongue, throat, and feet. In some reported cases, reactions were life-threatening and required emergency treatment. If a patient develops signs or symptoms of anaphylaxis or angioedema, levetiracetam should be discontinued and the patient should seek immediate medical attention. Levetiracetam should be discontinued permanently if a clear alternative etiology for the reaction cannot be established (see section 4.3).

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 drug related. 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 studies. A total of 3.4% of adult levetiracetam-treated patients experienced coordination difficulties, (reported as either ataxia, abnormal gait, or incoordination) compared to 1.6% of placebo patients. A total of 0.4% of patients in controlled trials discontinued levetiracetam treatment due to ataxia, compared to 0% of placebo patients. In 0.7% of treated patients and in 0.2% of placebo patients the dose was reduced due to coordination difficulties, while one of the treated patients was hospitalized due to worsening of pre-existing ataxia. 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 levetiracetam to gauge whether it adversely affects their ability to drive or operate machinery.

Withdrawal Seizures

As with most antiepileptic drugs, levetiracetam should be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus. But if withdrawal is needed because of a serious adverse reaction, rapid discontinuation can be considered.

Hematologic Abnormalities

Levetiracetam can cause hematologic abnormalities. Hematologic abnormalities occurred in clinical trials and included decreases in white blood cell (WBC), neutrophil, and red blood cells counts (RBC); decreases in hemoglobin and hematocrit; and increases in eosinophil counts. Cases of agranulocytosis, pancytopenia, and thrombocytopenia have been reported in the postmarketing setting. A complete blood count is recommended in patients experiencing significant weakness, pyrexia, recurrent infections, or coagulation disorders.

Partial-Onset Seizures

In controlled clinical studies using an oral formulation of levetiracetam in adult patients with partial-onset seizures, minor but statistically significant decreases compared to placebo in total mean RBC (0.03×10^6 /mm³), mean hemoglobin (0.09 g/dL), and mean hematocrit (0.38%), were seen in levetiracetam-treated patients.

A total of 3.2% of levetiracetam-treated and 1.8% of placebo-treated patients had at least one possibly significant ($\leq 2.8 \times 10^9$ /L) decreased WBC, and 2.4% of levetiracetam treated and 1.4% of placebo-treated patients had at least one possibly significant ($\leq 1.0 \times 10^9$ /L) decreased neutrophil count. Of the levetiracetam-treated patients with a low neutrophil count, all but one rose towards or to baseline with continued treatment. No patient was discontinued secondary to low neutrophil counts.

Juvenile Myoclonic Epilepsy

Although there were no obvious hematologic abnormalities observed in patients with JME, the limited number of patients 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.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro data on metabolic interactions indicate that levetiracetam is unlikely to produce, or be subject to, pharmacokinetic interactions. Levetiracetam and its major metabolite, at concentrations well above C levels achieved within the therapeutic dose range, are neither inhibitors of nor high affinity substrates for human liver cytochrome P450 isoforms, epoxide hydrolase or UDP-glucuronidation enzymes.

In addition, levetiracetam does not affect the in vitro glucuronidation of valproic acid.

Potential pharmacokinetic interactions of or with levetiracetam were assessed in clinical pharmacokinetic studies (phenytoin, valproate, warfarin, digoxin, oral contraceptive, probenecid) and through pharmacokinetic screening in the placebo-controlled clinical studies in epilepsy patients.

Phenytoin

Levetiracetam (3000 mg daily) had no effect on the pharmacokinetic disposition of phenytoin in patients with refractory epilepsy. Pharmacokinetics of levetiracetam were also not affected by phenytoin.

Valproate

Levetiracetam (1500 mg twice daily) did not alter the pharmacokinetics of valproate in healthy volunteers. 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, ucb L057.

Other Antiepileptic Drugs

Potential drug interactions between levetiracetam and other AEDs (carbamazepine, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone and valproate) were also assessed by evaluating the serum concentrations of levetiracetam and these AEDs during placebo-controlled clinical studies. These data indicate that 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 (ECG) 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^{ss} of the metabolite, ucb L057, was approximately doubled in the presence of probenecid while the fraction of drug excreted unchanged in the urine remained the same. Renal clearance of ucb L057 in the presence of probenecid decreased 60%, probably related to competitive inhibition of tubular secretion of ucb L057. The effect of levetiracetam on probenecid was not studied.

4.6 Fertility, pregnancy and lactation

Prolonged experience with levetiracetam in pregnant women has not identified a drug associated risk of major birth defects or miscarriage, based on published literature, which includes data from pregnancy registries and reflects experience over two decades. In animal studies, levetiracetam produced developmental toxicity (increased embryofetal and offspring mortality, increased incidences of fetal structural abnormalities, decreased embryofetal and offspring growth, neurobehavioral alterations in offspring) at doses similar to human therapeutic doses.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Clinical Considerations

Levetiracetam blood levels may decrease during pregnancy (see section 4.4).

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. Dose adjustments may be necessary to maintain clinical response.

Data

Human Data

While available studies cannot definitively establish the absence of risk, data from the published literature and pregnancy registries have not established an association with levetiracetam use during pregnancy and major birth defects or miscarriage.

Animal Data

When levetiracetam (0, 400, 1200, or 3600 mg/kg/day) was administered orally to pregnant rats during the period of organogenesis, reduced fetal weights and increased incidence of fetal skeletal variations were observed at the highest dose tested.

There was no evidence of maternal toxicity. The no-effect dose for adverse effects on embryofetal development in rats (1200 mg/kg/day) is approximately 4 times the maximum recommended human dose (MRHD) of 3000 mg on a body surface area (mg/m²) basis.

Oral administration of levetiracetam (0, 200, 600, or 1800 mg/kg/day) to pregnant rabbits during the period of organogenesis resulted in increased embryofetal mortality and incidence of fetal skeletal variations at the mid and high dose and decreased fetal weights and increased incidence of fetal malformations at the high dose, which was associated with maternal toxicity. The no-effect dose for adverse effects on embryofetal development in rabbits (200 mg/kg/day) is approximately equivalent to the MRHD on a mg/m² basis.

Oral administration of levetiracetam (0, 70, 350, or 1800 mg/kg/day) to female rats throughout pregnancy and lactation led to an increased incidence of fetal skeletal variations, reduced fetal body weight, and decreased growth in offspring at the mid and high doses and increased pup mortality and neurobehavioral alterations in offspring at the highest dose tested. There was no evidence of maternal toxicity. The no-effect dose for adverse effects on pre- and postnatal development in rats (70 mg/kg/day) is less than the MRHD on a mg/m² basis.

Oral administration of levetiracetam to rats during the latter part of gestation and throughout lactation produced no adverse developmental or maternal effects at doses of up to 1800 mg/kg/day (6 times the MRHD on a mg/m² basis).

Lactation

Risk Summary

Levetiracetam is excreted in human milk. There are no data on the effects of levetiracetam on the breastfed infant, or the effects on milk production.

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for levetiracetam and any potential adverse effects on the breastfed infant from levetiracetam or from the underlying maternal condition.

4.7 Effects on ability to drive and use machines

Inform patients that levetiracetam may cause dizziness and somnolence. Inform patients not to drive or operate machinery until they have gained sufficient experience on levetiracetam to gauge whether it adversely affects their ability to drive or operate machinery (see section 4.4).

4.8 Undesirable effects

The following serious adverse reactions are discussed in more details in other sections of labelling:

- Psychiatric Reactions (see section 4.4)
- Somnolence and Fatigue (see section 4.4)
- Anaphylaxis and Angioedema (see section 4.4)
- Serious Dermatological Reactions (see section 4.4)
- Coordination Difficulties (see section 4.4)
- Withdrawal Seizures (see section 4.4)
- Hematologic Abnormalities (see section 4.4)
- Seizure Control During Pregnancy (see section 4.4)

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The adverse reactions that result from levetiracetam injection use include all of those reported for levetiracetam tablets and oral solution. Equivalent doses of intravenous (IV) levetiracetam and oral levetiracetam result in equivalent C_{max} , C_{min} , and total systemic exposure to levetiracetam when the IV levetiracetam is administered as a 15-minute infusion.

Partial-Onset Seizures

In controlled clinical studies using levetiracetam tablets in adults with partial-onset seizures, the most common adverse reactions in adult patients receiving levetiracetam in combination with other AEDs, for events with rates greater than placebo, were somnolence, asthenia, infection and dizziness.

Of the most common adverse reactions in adults experiencing partial-onset seizures, asthenia, somnolence and dizziness occurred predominantly during the first 4 weeks of treatment with levetiracetam.

Table 2 lists adverse reactions that occurred in at least 1% of adult epilepsy patients receiving levetiracetam tablets in placebo-controlled studies and were numerically more common than in patients treated with placebo. In these studies, either levetiracetam or placebo was added to concurrent AED therapy. Adverse reactions were usually mild to moderate in intensity.

Table 2: Adverse Reactions* In Placebo-Controlled, Adjunctive Studies In Adults Experiencing Partial-Onset Seizures

Adverse Reaction	Levetiracetam (N=769) %	Placebo (N=439) %
Asthenia	15	9
Somnolence	15	8
Headache	14	13

Infection	13	8
Dizziness	9	4
Pain	7	6
Pharyngitis	6	4
Depression	4	2
Nervousness	4	2
Rhinitis	4	3
Anorexia	3	2
Ataxia	3	1
Vertigo	3	1
Amnesia	2	1
Anxiety	2	1
Cough Increased	2	1
Diplopia	2	1
Emotional Lability	2	0
Hostility	2	1
Paresthesia	2	1
Sinusitis	2	1

*Adverse reactions occurred in at least 1% of levetiracetam-treated patients and occurred more frequently than placebo-treated patients

In controlled adult clinical studies using levetiracetam tablets, 15% of patients receiving levetiracetam and 12% receiving placebo either discontinued or had a dose reduction as a result of an adverse reaction. Table 3 lists the most common (>1%) adverse reactions that resulted in discontinuation or dose reduction and that occurred more frequently in levetiracetam-treated patients than in placebo-treated patients.

Table 3: Adverse Reactions that Resulted in Discontinuation or Dose Reduction in Placebo-Controlled Studies in Adults Experiencing Partial-Onset Seizures

Adverse Reaction	Levetiracetam (N=769) %	Placebo (N=439) %
Somnolence	4	2
Dizziness	1	0

Myoclonic Seizures

Although the pattern of adverse reactions in this study seems somewhat different from that seen in patients with partial seizures, this is likely due to the much smaller number of patients in this study compared to partial seizure studies. The adverse reaction pattern for patients with JME is expected to be essentially the same as for patients with partial seizures.

In the controlled clinical study using levetiracetam tablets in patients with myoclonic seizures, the most common adverse reactions in patients using levetiracetam in combination with other AEDs, for events with rates greater than placebo, were somnolence, neck pain, and pharyngitis.

Table 4 lists adverse reactions that occurred in at least 5% of juvenile myoclonic epilepsy patients experiencing myoclonic seizures treated with levetiracetam tablets and were numerically more common than in patients treated with placebo. In this study, either levetiracetam or placebo was added to concurrent AED therapy. Adverse reactions were usually mild to moderate in intensity.

Table 4: Adverse Reactions in a Placebo-Controlled, Adjunctive Study in Patients 12 Years of Age and Older with Myoclonic Seizures

Adverse Reaction	Levetiracetam (N=60) %	Placebo (N=60) %
Somnolence	12	2
Neck pain	8	2
Pharyngitis	7	0
Depression	5	2
Influenza	5	2
Vertigo	5	3

* Adverse reactions occurred in at least 5% of levetiracetam-treated patients and occurred more frequently than placebo-treated patients

In the placebo-controlled study using levetiracetam tablets in patients with JME, 8% of patients receiving levetiracetam and 2% receiving placebo either discontinued or had a dose reduction as a result of an adverse reaction. The adverse reactions that led to discontinuation or dose reduction and that occurred more frequently in levetiracetam treated patients than in placebo-treated patients are presented in Table 5.

Table 5: Adverse Reactions that Resulted in Discontinuation or Dose Reduction in Patients with Juvenile Myoclonic Epilepsy

Adverse Reaction	Levetiracetam (N=60) %	Placebo (N=60) %
Anxiety	3	2
Depressed mood	2	0
Depression	2	0
Diplopia	2	0
Hypersomnia	2	0
Insomnia	2	0
Irritability	2	0

Nervousness	2	0
Somnolence	2	0

Primary Generalized Tonic-Clonic Seizures

Although the pattern of adverse reactions in this study seems somewhat different from that seen in patients with partial seizures, this is likely due to the much smaller number of patients in this study compared to partial seizure studies. The adverse reaction pattern for patients with primary generalized tonic-clonic (PGTC) seizures is expected to be essentially the same as for patients with partial seizures.

In the controlled clinical study that included patients with PGTC seizures, the most common adverse reaction in patients receiving levetiracetam oral formulation in combination with other AEDs, for events with rates greater than placebo was nasopharyngitis.

Table 6 lists adverse reactions that occurred in at least 5% of idiopathic generalized epilepsy patients experiencing PGTC seizures treated with levetiracetam and were numerically more common than in patients treated with placebo. In this study, either levetiracetam or placebo was added to concurrent AED therapy.

Table 6: Adverse Reactions in a Placebo-Controlled, Adjunctive Study in Patients with PGTC Seizures

Adverse Reaction	Levetiracetam (N=79) %	Placebo (N=84) %
Nasopharyngitis	14	5
Fatigue	10	8
Diarrhea	8	7
Irritability	6	2
Mood swings	5	1

* Adverse reactions occurred in at least 5% of levetiracetam-treated patients and occurred more frequently than placebo-treated patients

In the placebo-controlled study, 5% of patients receiving levetiracetam and 8% receiving placebo either discontinued or had a dose reduction during the treatment period as a result of an adverse reaction.

This study was too small to adequately characterize the adverse reactions that could be expected to result in discontinuation of treatment in this population. It is expected that the adverse reactions that would lead to discontinuation in this population would be similar to those resulting in discontinuation in other epilepsy trials (see Tables 3 and 5).

In addition, the following adverse reactions were seen in other controlled adult studies of levetiracetam: balance disorder, disturbance in attention, eczema, memory impairment, myalgia, and blurred vision.

Comparison of Gender, Age and Race

The overall adverse reaction profile of levetiracetam was similar between females and males. There are insufficient data to support a statement regarding the distribution of adverse reactions by age and race.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of levetiracetam. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In addition to the adverse reactions listed above, the following adverse reactions have been reported in patients receiving marketed levetiracetam worldwide. The listing is alphabetized: abnormal liver function test, acute kidney injury, agranulocytosis, anaphylaxis, angioedema, choreoathetosis, drug reaction with eosinophilia and systemic symptoms (DRESS), dyskinesia, erythema multiforme, hepatic failure, hepatitis, hyponatremia, muscular weakness, pancreatitis, pancytopenia (with bone marrow suppression identified in some of these cases), panic attack, thrombocytopenia, weight loss, and worsening of seizures. Alopecia has been reported with levetiracetam use; recovery was observed in majority of cases where levetiracetam was discontinued.

Reporting 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 via Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org/>

4.9 Overdose

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans

The highest known dose of oral levetiracetam received in the clinical development program was 6000 mg/day. Other than drowsiness, there were no adverse reactions in the few known cases of overdose in clinical trials. Cases of somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with levetiracetam overdoses in postmarketing 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. A Certified Poison Control Center should be contacted for up to date information on the management of overdose with levetiracetam.

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

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

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 precise mechanism(s) by which levetiracetam exerts its antiepileptic effect is unknown.

A saturable and stereoselective neuronal binding site in rat brain tissue has been described for levetiracetam. Experimental data indicate that this binding site is the synaptic vesicle protein SV2A, thought to be involved in the regulation of vesicle exocytosis. Although the molecular significance of levetiracetam binding to synaptic vesicle protein SV2A is not understood, levetiracetam and related analogs showed a rank order of affinity for SV2A which correlated with the potency of their antiseizure activity in audiogenic seizure-prone mice. These findings suggest that the interaction of levetiracetam with the SV2A protein may contribute to the antiepileptic mechanism of action of the drug.

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.

5.2 Pharmacokinetic properties

Equivalent doses of intravenous (IV) levetiracetam and oral levetiracetam result in equivalent C_{max}, C_{min}, and total systemic exposure to levetiracetam when the IV levetiracetam is administered as a 15 minute infusion.

Overview

Levetiracetam is rapidly and almost completely absorbed after oral administration. Levetiracetam injection and tablets are bioequivalent. The pharmacokinetics of levetiracetam are linear and time-invariant, with low intra- and inter-subject variability. Levetiracetam is not significantly protein-bound (<10% bound) and its volume of distribution is close to the volume of intracellular and extracellular water. Sixty-six percent (66%) of the dose is renally excreted unchanged. The major metabolic pathway of levetiracetam (24% of dose) is an enzymatic hydrolysis of the acetamide group. It is not liver cytochrome P450 dependent. The metabolites have no known pharmacological activity and are renally excreted. Plasma half-life of levetiracetam across studies is approximately 6-8 hours. It is increased in the elderly (primarily due to impaired renal clearance) and in subjects with renal impairment.

Distribution

The equivalence of levetiracetam injection and the oral formulation was demonstrated in a bioavailability study of 17 healthy volunteers. In this study, levetiracetam 1500 mg was diluted in 100 mL 0.9% sterile saline solution and was infused over 15 minutes. The selected infusion rate provided plasma concentrations of levetiracetam at the end of the infusion period similar to those achieved at T_{max} after an equivalent oral dose. It is demonstrated that levetiracetam 1500 mg intravenous infusion is equivalent to levetiracetam 3 x 500 mg oral tablets. The time independent pharmacokinetic profile of levetiracetam was demonstrated following 1500 mg intravenous infusion for 4 days with BID dosing. The AUC (0-12) at steady-state was equivalent to AUC_{inf} following an equivalent single dose.

Levetiracetam and its major metabolite are less than 10% bound to plasma proteins; clinically significant interactions with other drugs through competition for protein binding sites are therefore unlikely.

Metabolism

Levetiracetam is not extensively metabolized in humans. The major metabolic pathway is the enzymatic hydrolysis of the acetamide group, which produces the carboxylic acid metabolite, ucb L057 (24% of dose) and is not dependent on any liver cytochrome P450 isoenzymes. The major metabolite is inactive in animal seizure models. Two minor metabolites were identified as the product of hydroxylation of the 2-oxo-pyrrolidine ring (2% of dose) and opening of the 2-oxo-pyrrolidine ring in position 5 (1% of dose). There is no enantiomeric interconversion of levetiracetam or its major metabolite.

Elimination

Levetiracetam plasma half-life in adults is 7 ± 1 hour and is unaffected by either dose, route of administration or repeated administration. Levetiracetam is eliminated from the systemic circulation by renal excretion as unchanged drug which represents 66% of administered dose. The total body clearance is 0.96 mL/min/kg and the renal clearance is 0.6 mL/min/kg. The mechanism of excretion is glomerular filtration with subsequent partial tubular reabsorption. The metabolite ucb L057 is excreted by glomerular filtration and active tubular secretion with a renal clearance of 4 mL/min/kg. Levetiracetam elimination is correlated to creatinine clearance. Levetiracetam clearance is reduced in patients with renal impairment

Specific Populations

Elderly

Pharmacokinetics of levetiracetam were evaluated in 16 elderly subjects (age 61-88 years) with creatinine clearance ranging from 30 to 74 mL/min. Following oral administration of twice-daily dosing for 10 days, total body clearance decreased by 38% and the half-life was 2.5 hours longer in the elderly compared to healthy adults. This is most likely due to the decrease in renal function in these subjects.

Pregnancy

Levetiracetam levels may decrease during pregnancy (see section 4.4 and see section 4.6).

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.

Renal Impairment

The disposition of levetiracetam was studied in adult subjects with varying degrees of renal function. Total body clearance of levetiracetam is reduced in patients with impaired renal function by 40% in the mild group (CL_{cr} = 50-80 mL/min), 50% in the moderate group (CL_{cr} = 30-50 mL/min) and 60% in the severe renal impairment group (CL_{cr} <30 mL/min). Clearance of levetiracetam is correlated with creatinine clearance.

In anuric (end stage renal disease) patients, the total body clearance decreased 70% compared to normal subjects (CL_{cr} >80mL/min). Approximately 50% of the pool of levetiracetam in the body is removed during a standard 4 hour hemodialysis procedure

Hepatic Impairment

In subjects with mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment, the pharmacokinetics of levetiracetam were unchanged. In patients 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 for patients with hepatic impairment.

5.3 Preclinical safety data

Carcinogenesis

Rats were dosed with levetiracetam in the diet for 104 weeks at doses of 50, 300 and 1800 mg/kg/day. Plasma exposure (AUC) at the highest dose was approximately 6 times that in humans at the maximum recommended human dose (MRHD) of 3000 mg. There was no evidence of carcinogenicity. In mice, oral administration of levetiracetam for 80 weeks (doses up to 960 mg/kg/day) or 2 years (doses up to 4000 mg/kg/day, lowered to 3000 mg/kg/day after 45 weeks due to intolerability) was not associated with an increase in tumors. The highest dose tested in mice for 2 years (3000 mg/kg/day) is approximately 5 times the MRHD on a body surface area (mg/m²) basis.

Mutagenesis

Levetiracetam was negative in *in vitro* (Ames, chromosomal aberration in mammalian cells) and *in vivo* (mouse micronucleus) assays. The major human metabolite of levetiracetam (ucb L057) was negative in *in vitro* (Ames, mouse lymphoma) assays.

Impairment of Fertility

No adverse effects on male or female fertility or reproductive performance were observed in rats at oral doses up to 1800 mg/kg/day, which were associated with plasma exposures (AUC) up to approximately 6 times that in humans at the MRHD.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium chloride, Sodium acetate trihydrate, Glacial acetic acid, Water for Injection.

6.2 List of excipients

Levetiracetam in 0.82% Sodium Chloride Injection should not be further diluted prior to its use.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C. Do not freeze. Protect from light.

6.5 Nature and contents of container

Levetiracetam in 0.82% Sodium Chloride Injection, EPIEND is available as 100 ml in Non PVC bag. Non PVC bag is overwrapped with metallic pouch and packed in monocarton along with pack insert.

6.6 Special precautions for disposal and other handling

This medicinal product is for single use only. Medicinal product with particulate matter or discoloration should not be used.

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

7. Marketing authorisation holder

Otsuka Pharmaceutical India Private
Limited Village-Vasana-
Chacharwadi, Tal - Sanand, Dist:
Ahmedabad - 382 213, India.

8. Marketing authorisation number(s)

H2025/CTD11677/24281

9. Date of first Registration/renewal of the Registration

2025 March 06

10. Date of revision of the text

01/08/2026