

For use of a Registered Medical Practitioner only
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1. Generic Name and Brand Name

Levetiracetam Oral Solution I.P. 500 mg

Levesam®

2. Qualitative and Quantitative Composition:

Each 5 ml contains:

Levetiracetam I.P.....500 mg

In Flavoured Syrup base.....q.s.

3. Dosage Form & strength

Refer section 1 & 2

4. Clinical particulars**4.1 Therapeutic indication**

As Adjunctive Therapy in the Treatment of Partial Onset Seizures With or Without Secondary Generalisation in Adults, Children and Infants from 1 month of age with epilepsy.

4.2 Posology and method of administrationPediatric Patients:*Pediatric Patients 1 Month to < 6 Months:*

Initiate treatment with a daily dose of 14 mg/kg in 2 divided doses (7 mg/kg twice daily). Increase the daily dose every 2 weeks by increments of 14 mg/kg to the recommended daily dose of 42 mg/kg (21 mg/kg twice daily). In the clinical trial, the mean daily dose was 35 mg/kg in this age group.

6 Months to < 4 Years:

Initiate treatment with a daily dose of 20 mg/kg in 2 divided doses (10 mg/kg twice daily). Increase the daily dose in 2 weeks by an increment of 20 mg/kg to the recommended daily dose of 50 mg/kg (25 mg/kg twice daily). If a patient cannot tolerate a daily dose of 50 mg/kg, the daily dose may be reduced. In the clinical trial, the mean daily dose was 47 mg/kg in this age group.

Ages 4 To <16 Years:

Treatment should be initiated with a daily dose of 20 mg/kg in 2 divided doses (10 mg/kg BID). The daily dose should be increased every 2 weeks by increments of 20 mg/kg to the recommended daily dose of 60 mg/kg (30 mg/kg BID). If a patient cannot tolerate a daily dose of 60 mg/kg, the daily dose may be reduced. Patients with body weights 20 kg should be dosed with oral solution.

Levetiracetam is given orally with or without food.

The following calculation should be used to determine the appropriate daily dose of oral solution for pediatric patients based on a daily dose of 20 mg/kg/day, 40 mg/kg/day or 60 mg/kg/day:

$$\text{Total daily dose ml/day} = \frac{\text{Daily dose(mg/kg/day)} \times \text{patient weight (kg)}}{100 \text{ mg/ml}}$$

Adults 16 years and older:

Treatment should be initiated with a daily dose of 1000 mg/day, given as twice-daily dosing (500 mg BID). 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 for periods of 6 months and longer. There is no evidence that doses greater than 3000 mg/day confer additional benefit.

Patients with Impaired Renal Function:

Recommended doses and adjustment for dose for adults are shown in table below. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in mL/min is needed. CLcr in mL/min may be estimated from serum creatinine (mg/dL) determination using the following formula:

$$\text{CLcr} = \frac{[140 - \text{age (years)}] \times \text{body weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

To account for females, CLcr determined from above equation should be multiplied by 0.85.

Creatinine clearance (mL/min)	Daily Dose (mg/day)	Dose Regimen
≥80	500-1500	Every 12 h
50-80	500-1000	Every 12 h
30-50	250-750	Every 12 h
<30	250-500	Every 12 h
ESRD patients on dialysis	500-1000	Every 24 h*

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

4.3 Contraindications

Levetiracetam is contraindicated in those hypersensitive to levetiracetam or any of its components. Reactions have included anaphylaxis and angioedema

4.4 Special warnings and precautions for use

4.4.1 Behavioral Abnormalities and Psychotic Symptoms

Levetiracetam may cause behavioral abnormalities and psychotic symptoms. Patients treated with Levetiracetam should be monitored for psychiatric signs and symptoms.

Behavioral abnormalities

In clinical studies, 13% of adult Levetiracetam-treated patients and 38% of pediatric Levetiracetam-treated patients (4 to 16 years of age) compared to 6% and 19% of adult and pediatric placebo-treated patients, experienced non-psychotic behavioral symptoms (reported as aggression, agitation, anger, anxiety, apathy, depersonalization, depression, emotional lability, hostility, hyperkinesias, irritability, nervousness, neurosis, and personality disorder).

A randomized double-blind, placebo-controlled study was performed to assess the neurocognitive and behavioral effects of Levetiracetam as adjunctive therapy in pediatric patients (4 to 16 years of age). The results from an exploratory analysis indicated a worsening in Levetiracetam-treated patients on aggressive behavior (one of eight behavior dimensions) as measured in a standardized

and systematic way using a validated instrument, the Achenbach Child Behavior Checklist (CBCL/6-18).

In clinical studies in pediatric patients 1 month to < 4 years of age, irritability was reported in 12% of the Levetiracetam-treated patients compared to 0% of placebo-treated patients.

In clinical studies, 1.7% of adult Levetiracetam-treated patients discontinued treatment due to behavioral adverse reactions, compared to 0.2% of placebo-treated patients. The treatment dose was reduced in 0.8% of adult Levetiracetam-treated patients and in 0.5% of placebo-treated patients. Overall, 11% of Levetiracetam-treated pediatric patients experienced behavioral symptoms associated with discontinuation or dose reduction, compared to 6% of placebo-treated patients.

Psychotic symptoms

In clinical studies, 1% of Levetiracetam-treated adult patients, 2% of Levetiracetam-treated pediatric patients 4 to 16 years of age, and 17% of Levetiracetam-treated pediatric patients 1 month to <4 years of age experienced psychotic symptoms, compared to 0.2%, 2%, and 5% in the corresponding age groups treated with placebo. In a controlled study that assessed the neurocognitive and behavioral effects of Levetiracetam in pediatric patients 4 to 16 years of age, 1.6% of Levetiracetam-treated patients experienced paranoia, compared to 0% of placebo-treated patients. In the same study, 3.1% of Levetiracetam-treated patients experienced confusional state, compared to 0% of placebo-treated patients.

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

4.4.2 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including Levetiracetam, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono-and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed. Table 2 shows absolute and relative risk by indication for all evaluated AEDs.

Table 2: Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing Levetiracetam or any other AED must balance the risk of suicidal thoughts or behaviors with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

4.4.3 Somnolence and Fatigue

Levetiracetam may cause somnolence and fatigue. 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.

Somnolence

In controlled trials of adult patients with epilepsy experiencing partial-onset seizures, 15% of Levetiracetam-treated patients reported somnolence, compared to 8% of placebo-treated 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 Levetiracetam-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-treated patients. In 1.4% of Levetiracetam-treated patients and 0.9% of placebo-treated patients, the dose was reduced, while 0.3% of the Levetiracetam-treated patients were hospitalized due to somnolence.

Asthenia

In controlled clinical studies of adult patients with epilepsy experiencing partial-onset seizures, 15% of Levetiracetam-treated patients reported asthenia, compared to 9% of placebo-treated patients. Treatment was discontinued due to asthenia in 0.8% of Levetiracetam-treated patients as compared to 0.5% of placebo-treated patients. In 0.5% of Levetiracetam-treated patients and in 0.2% of placebo-treated patients, the dose was reduced due to asthenia.

Somnolence and asthenia occurred most frequently within the first 4 weeks of treatment. In general, the incidences of somnolence and fatigue in the pediatric partial-onset seizure studies, and in pediatric and adult myoclonic and primary generalized tonic-clonic seizure studies were comparable to those of the adult partial-onset seizure studies.

4.4.4 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 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.

4.4.5 Serious Dermatological Reactions

Serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in both pediatric and adult 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.

4.4.6 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multiorgan hypersensitivity, has been reported in patients taking antiepileptic drugs, including Levetiracetam. These events can be fatal or life-threatening, particularly if diagnosis and treatment do not occur as early as possible. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis, sometimes resembling an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its expression, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Levetiracetam should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

4.4.7 Coordination Difficulties

Levetiracetam may cause coordination difficulties.

In controlled clinical studies in adult patients with partial-onset seizure studies, 3.4% of adult Levetiracetam-treated patients experienced coordination difficulties, (reported as either ataxia, abnormal gait, or incoordination) compared to 1.6% of placebo-treated patients. A total of 0.4% of patients in controlled clinical studies discontinued Levetiracetam treatment due to ataxia, compared to 0% of placebo-treated patients. In 0.7% of Levetiracetam-treated patients and in 0.2% of placebo-treated patients, the dose was reduced due to coordination difficulties, while one of the Levetiracetam-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 could adversely affect their ability to drive or operate machinery.

4.4.8 Withdrawal Seizures

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

4.4.9 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 cell (RBC) counts; 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

Adults

Minor, but statistically significant, decreases compared to placebo in total mean RBC count ($0.03 \times 10^6/\text{mm}^3$), mean hemoglobin (0.09 g/dL), and mean hematocrit (0.38%), were seen in Levetiracetam-treated patients in controlled trials.

A total of 3.2% of Levetiracetam-treated and 1.8% of placebo-treated patients had at least one possibly significant ($\leq 2.8 \times 10^9/\text{L}$) decreased WBC, and 2.4% of Levetiracetam-treated and 1.4% of placebo-treated patients had at least one possibly significant ($\leq 1.0 \times 10^9/\text{L}$) 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.

Pediatric Patients 4 Years to < 16 Years

Statistically significant decreases in WBC and neutrophil counts were seen in Levetiracetam-treated patients as compared to placebo. The mean decreases from baseline in the Levetiracetam-treated group were $-0.4 \times 10^9/\text{L}$ and $-0.3 \times 10^9/\text{L}$, respectively, whereas there were small increases in the placebo group. Mean relative lymphocyte counts increased by 1.7% in Levetiracetam-treated patients, compared to a decrease of 4% in placebo patients (statistically significant).

In the controlled trial, more Levetiracetam-treated patients had a possibly clinically significant abnormally low WBC value (3% of Levetiracetam-treated patients versus 0% of placebo-treated patients), however, there was no apparent difference between treatment groups with respect to neutrophil count (5% of Levetiracetam-treated patients versus 4.2% of placebo-treated patients). No patient was discontinued secondary to low WBC or neutrophil counts.

In the controlled cognitive and neuropsychological safety study, 5 patients (8.6%) in the Levetiracetam-treated group and two patients (6.1%) in the placebo-treated group had high eosinophil count values that were possibly clinically significant ($\geq 10\%$ or $\geq 0.7 \times 10^9/L$).

4.4.10 Increase in Blood Pressure

In a randomized, placebo-controlled study in patients 1 month to <4 years of age, a significantly higher risk of increased diastolic blood pressure was observed in the Levetiracetam-treated patients (17%), compared to the placebo-treated patients (2%). There was no overall difference in mean diastolic blood pressure between the treatment groups. This disparity between the Levetiracetam and placebo treatment groups was not observed in the studies of older children or in adults.

Monitor patients 1 month to <4 years of age for increases in diastolic blood pressure.

4.4.11 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.

4.4.12 Electrocardiogram QT interval prolongation

Rare cases of ECG QT interval prolongation have been observed during the post-marketing surveillance. Levetiracetam should be used with caution in patients with QTc-interval prolongation, in patients concomitantly treated with drugs affecting the QTc-interval, or in patients with relevant pre-existing cardiac disease or electrolyte disturbances.

4.5 Drug Interactions

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_{max} 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.

Effect of AEDs in Pediatric Patients

There was about a 22% increase of apparent total body clearance of Levetiracetam when it was co-administered with enzyme-inducing AEDs. Dose adjustment is not recommended. Levetiracetam had no effect on plasma concentrations of carbamazepine, valproate, topiramate, or lamotrigine.

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. Coadministration 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. Coadministration 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. Coadministration 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,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 Use in special populations (Pregnancy, Nursing woman, Pediatric use, Geriatric use)

4.6.1 Pregnancy

Risk Summary

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.

Clinical Considerations

Levetiracetam blood levels may decrease during pregnancy.

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 developmental 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).

4.6.2 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 developmental 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.

4.6.3 Pediatric Use

The safety and effectiveness of Levetiracetam for the treatment of partial-onset seizures in patients 1 month to 16 years of age have been. The dosing recommendation in these pediatric patients varies according to age group and is weight-based.

The safety and effectiveness of Levetiracetam as adjunctive therapy for the treatment of myoclonic seizures in adolescents 12 years of age and older with juvenile myoclonic epilepsy have been established.

The safety and effectiveness of Levetiracetam as adjunctive therapy for the treatment of primary generalized tonic-clonic seizures in pediatric patients 6 years of age and older with idiopathic generalized epilepsy have been established.

Safety and effectiveness for the treatment of partial-onset seizures in pediatric patients below the age of 1 month; adjunctive therapy for the treatment of myoclonic seizures in pediatric patients below the age of 12 years; and adjunctive therapy for the treatment of primary generalized tonic-clonic seizures in pediatric patients below the age of 6 years have not been established.

A 3-month, randomized, double-blind, placebo-controlled study was performed to assess the neurocognitive and behavioral effects of Levetiracetam as adjunctive therapy in 98 (Levetiracetam N=64, placebo N=34) pediatric patients, ages 4 to 16 years old, with partial seizures that were inadequately controlled. The target dose was 60 mg/kg/day. Neurocognitive effects were measured by the Leiter-R Attention and Memory (AM) Battery, which measures various aspects of a child's memory and attention. Although no substantive differences were observed between the placebo and drug treated groups in the median change from baseline in this battery, the study was not adequate to assess formal statistical non-inferiority of the drug and placebo. The Achenbach Child Behavior Checklist (CBCL/6-18), a standardized validated tool used to assess a child's competencies and behavioral/emotional problems, was also assessed in this study. An analysis of the CBCL/6-18 indicated on average a worsening in Levetiracetam-treated patients in aggressive behavior, one of the eight syndrome scores.

Juvenile Animal Toxicity Data

Studies of Levetiracetam in juvenile rats (dosed on postnatal days 4 through 52) and dogs (dosed from postnatal weeks 3 through 7) at doses of up to 1800 mg/kg/day (approximately 7 and 24 times, respectively, the maximum recommended pediatric dose of 60 mg/kg/day on a mg/m² basis) did not demonstrate adverse effects on postnatal development.

4.6.4 Geriatric Use

There were 347 subjects in clinical studies of Levetiracetam that were 65 and over. No overall differences in safety were observed between these subjects and younger subjects. There were insufficient numbers of elderly subjects in controlled trials of epilepsy to adequately 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.

4.6.5 Renal Impairment

Clearance of Levetiracetam is decreased in patients with renal impairment and is correlated with creatinine clearance. Dose adjustment is recommended for patients with impaired renal function and supplemental doses should be given to patients after dialysis.

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

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

- Behavior Abnormalities and Psychotic Symptoms
- Suicidal Behavior and Ideation
- Somnolence and Fatigue
- Anaphylaxis and Angioedema
- Serious Dermatological Reactions
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity
- Coordination Difficulties
- Hematologic Abnormalities
- Increase in Blood Pressure

MEDRA SOC	Frequency category				
	Very common	Common	Uncommon	Rare	Very rare
Infections and infestations	Nasopharyngitis			Infection	
Blood and lymphatic system disorders			Thrombocytopenia, leukopenia	Pancytopenia, neutropenia, agranulocytosis	

Immune system disorders				Drug reaction with eosinophilia and systemic symptoms (DRESS), Hypersensitivity (including angioedema and anaphylaxis)	
Metabolism and nutrition disorders		Anorexia	Weight decreased, weight increase	Hyponatraemia	
Psychiatric disorders		Depression, hostility/aggression, anxiety, insomnia, nervousness/irritability	Suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusional state, panic attack, affect lability/mood swings, agitation	Completed suicide, personality disorder, thinking abnormal, delirium	Obsessive compulsive disorder*
Nervous system disorders	Somnolence, headache	Convulsion, balance disorder, dizziness, lethargy, tremor	Amnesia, memory impairment, coordination abnormal/ataxia, paraesthesia, disturbance in attention	Choreoathetosis, dyskinesia, hyperkinesia, gait disturbance, encephalopathy, seizures aggravated, Neuroleptic malignant syndrome**	
Eye disorders			Diplopia, vision blurred		
Ear and labyrinth disorders		Vertigo			

Cardiac disorders				Electrocardiogram QT prolonged	
Respiratory, thoracic and mediastinal disorders		Cough			
Gastrointestinal disorders		Abdominal pain, diarrhoea, dyspepsia, vomiting, nausea		Pancreatitis	
Hepatobiliary disorders			Liver function test abnormal	Hepatic failure, hepatitis	
Renal and Urinary Disorders				Acute Kidney injury	
Skin and subcutaneous tissue disorders		Rash	Alopecia, eczema, pruritus,	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme	
Musculoskeletal and connective tissue disorders			Muscular weakness, myalgia	Rhabdomyolysis and blood creatine phosphokinase increased**	
General disorders and administration site conditions		Asthenia/fatigue			
Injury, poisoning and procedural complications			Injury		

Tabulated list of adverse reactions

Adverse reactions reported in clinical studies (adults, adolescents, children and infants > 1 month) and from post-marketing experience are listed in the following table per System Organ Class and per frequency. Adverse reactions are presented in the order of decreasing seriousness and their frequency is defined as follows: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10000$ to $< 1/1000$) and very rare ($< 1/10000$).

*Very rare cases of development of obsessive-compulsive disorders (OCD) in patients with underlying history of OCD or psychiatric disorders have been observed in post-marketing surveillance.

**Prevalence is significantly higher in Japanese patients when compared to non-Japanese patients.

4.9 Overdose

There is no specific antidote for overdose with Levetiracetam. Immediate referral to the closest hospital or treatment center is recommended. 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.

5 Pharmacological properties

5.1 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 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.

5.2 Pharmacodynamic Properties

Effects on QTc Interval The effect of Levetiracetam on QTc prolongation was evaluated in a randomized, double-blind, positive-controlled (moxifloxacin 400 mg) and placebo-controlled crossover study of Levetiracetam (1000 mg or 5000 mg) in 52 healthy subjects. The upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc was below 10 milliseconds. Therefore, there was no evidence of significant QTc prolongation in this study.

5.3 Pharmacokinetic properties

The pharmacokinetics of Levetiracetam are similar when used as monotherapy or as adjunctive therapy for the treatment of partial-onset seizures.

Absorption and Distribution

Absorption of Levetiracetam is rapid, with peak plasma concentrations occurring in about an hour following oral administration in fasted subjects. The oral bioavailability of Levetiracetam tablets

is 100% and the tablets and oral solution are bioequivalent in rate and extent of absorption. Food does not affect the extent of absorption of Levetiracetam but it decreases C_{max} by 20% and delays T_{max} by 1.5 hours. The pharmacokinetics of Levetiracetam are linear over the dose range of 500-5000 mg. Steady state is achieved after 2 days of multiple twice-daily dosing. 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 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.

Pediatric Patients

Pharmacokinetics of Levetiracetam were evaluated in 24 pediatric patients (age 6-12 years) after single dose (20 mg/kg). The body weight adjusted apparent clearance of Levetiracetam was approximately 40% higher than in adults. A repeat dose pharmacokinetic study was conducted in pediatric patients (age 4-12 years) at doses of 20 mg/kg/day, 40 mg/kg/day, and 60 mg/kg/day. The evaluation of the pharmacokinetic profile of Levetiracetam and its metabolite (ucb L057) in 14 pediatric patients demonstrated rapid absorption of Levetiracetam at all doses with a T_{max} of about 1 hour and a t_{1/2} of 5 hours across the three dosing levels. The pharmacokinetics of Levetiracetam in children was linear between 20 to 60 mg/kg/day. The potential interaction of Levetiracetam with other AEDs was also evaluated in these patients. Levetiracetam had no significant effect on the plasma concentrations of carbamazepine, valproic acid, topiramate or

lamotrigine. However, there was about a 22% increase of apparent clearance of Levetiracetam when it was co-administered with an enzyme-inducing AED (e.g. carbamazepine). Following single dose administration (20 mg/kg) of a 10% oral solution to children with epilepsy (1 month to < 4 years), Levetiracetam was rapidly absorbed and peak plasma concentrations were observed approximately 1 hour after dosing. The pharmacokinetic results indicated that half-life was shorter (5.3 h) than for adults (7.2 h) and apparent clearance was faster (1.5 mL/min/kg) than for adults (0.96 mL/min/kg). Population pharmacokinetic analysis showed that body weight was significantly correlated to the clearance of Levetiracetam in pediatric patients; clearance increased with an increase in body weight.

Pediatric Patients with Obesity

A population PK analysis of Levetiracetam was conducted in 164 obese and non-obese pediatric patients 2 to <18 years of age with median (range) weight 39.2 (11.3-134) kg to evaluate the potential impact of obesity on plasma Levetiracetam exposures. Obesity was defined as BMI $\geq$ 95th percentile for age and sex based on CDC 2000 growth chart recommendations. Simulations were conducted for obese and non-obese pediatric patients ages 4 to <16 years.

- When the recommended tablet dose is administered to pediatric patients weighing < 40 kg, obese pediatric patients have 27% higher median $C_{max,ss}$ and 19% higher median $C_{min,ss}$ compared to non-obese patients.
- When the recommended tablet dose is administered to pediatric patients weighing $\geq$ 40 kg, obese pediatric patients have 10-11% lower median $C_{max,ss}$ and 2% lower median $C_{min,ss}$ compared to non-obese patients.
- When the recommended oral solution dose is administered to pediatric patients across the full weight range, obese pediatric patients have 25% higher median $C_{max,ss}$ and 41% higher median $C_{min,ss}$ compared to non-obese pediatric patients.

However, differences in exposures between obese and non-obese pediatric patients are not expected to be clinically meaningful because the recommended dose titration at initiation of Levetiracetam therapy would establish an appropriate dose for each individual patient.

Pregnancy

Levetiracetam levels may decrease during pregnancy

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 (CLcr = 50-80 mL/min), 50% in the moderate group (CLcr = 30-50 mL/min) and 60% in the severe renal impairment group (CLcr <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 (CLcr >80 mL/min). Approximately 50% of the pool of Levetiracetam in the body is removed during a standard 4hour hemodialysis procedure [see Dosage and Administration (2.5)].

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.

6 Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

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 daily 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.

7 Description

Levetiracetam is an antiepileptic drug available as a clear, colorless, flavored liquid (100 mg/ml) for oral administration.

8 Pharmaceutical particulars

8.1 Incompatibilities

NA

8.2 Shelf Life

Refer Pack

8.3 Packaging Information

One bottle of 100 ml Levesam Solution, measuring cup & AcuDDial syringe.

8.4 Storage condition & handling instructions

Store protected from light, at a temperature not exceeding 30°C.

Medicine: Keep out of reach of children.

Shake well before use.

9. Patient Counseling Information

Advise the patient to read the approved patient labeling.

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 psychotic symptoms.

Suicidal Behavior and Ideation:

Counsel patients, their caregivers, and/or families that antiepileptic drugs (AEDs), including Levetiracetam, 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.

Effects on Driving or Operating Machinery:

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.

Anaphylaxis and Angioedema:

Advise patients to discontinue Levetiracetam and seek medical care if they develop signs and symptoms of anaphylaxis or angioedema.

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.

DRESS/Multiorgan Hypersensitivity:

Instruct patients and caregivers that a fever or rash associated with signs of other organ system involvement (e.g., lymphadenopathy, hepatic dysfunction) may be drug-related and should be reported to their healthcare provider immediately. Levetiracetam should be discontinued immediately if a serious hypersensitivity reaction is suspected.

Withdrawal of Levetiracetam:

Advise patients and caregivers not to discontinue use of Levetiracetam without consulting with their healthcare provider.

Levetiracetam should normally be gradually withdrawn to reduce the potential of increased seizure frequency and status epilepticus.

Pregnancy:

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during Levetiracetam therapy.

10. Details of manufacturer

Manufactured by:

Tirupati Medicare Limited

Nahan Road, Paonta Sahib,

Dist. Sirmour (H.P.)-173 025, INDIA.

Marketed by:

Abbott Healthcare Pvt. Ltd.

Angel Space, Bldg. D-4, Gala No. 1 to 3 & 11 to 13 Ground Floor,
101 to 106 & 111 to 116 First Floor, 201 to 206 & 211 to 216 2nd
Floor, Pimpalas, Dist. Thane, Bhiwandi-421 302, Maharashtra, India.

®- Regd. Trademark of Abbott Healthcare Pvt. Ltd.

11. Details of permission or licence number with date

Mfg. Lic. No. MNB/07/552, dated 17-May-22

12. Date of revision

Version: 1.0, dated 16-Jun-26

For Product Complaints/Adverse events or Queries please write to
webmasterindia@abbott.com