PRESCRIBING INFORMATION

For the use of a registered medical practitioner or a hospital or a laboratory

Levera RTU 500 / 1000 / 1500

(Levetiracetam in Sodium Chloride Injection)

COMPOSITION

Levera RTU 500

Levetiracetam in 0.82% Sodium Chloride Injection, 500 mg/100 mL Infusion Bottle

Each 100 mL contains:

Levetiracetam IP	500 mg
Water for Injections IP	Q.S.

Levera RTU 1000

Levetiracetam in 0.75% Sodium Chloride Injection, 1000 mg/100 mL Infusion Bottle

Each 100 mL contains:

Levetiracetam IP	1000 mg
Water for Injections IP	Q.S.

Levera RTU 1500

Levetiracetam in 0.54% Sodium Chloride Injection, 1500 mg/100 mL Infusion Bottle

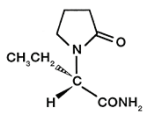
Each 100 mL contains:

Levetiracetam IP	1500 mg
Water for Injections IP	Q.S.

DESCRIPTION

Levera RTU (Levetiracetam in Sodium Chloride Injection) is a clear, colourless, sterile solution.

Levetiracetam is an antiepileptic drug. The chemical name of levetiracetam, a single enantiomer, is (-)-(*S*)-α-ethyl-2-oxo-1-pyrrolidine acetamide; its molecular formula is $C_8H_{14}N_2O_2$ and its molecular weight is 170.21. Levetiracetam is chemically unrelated to existing antiepileptic drugs (AEDs). The structural formula of levetiracetam is shown below (figure 1).



INDICATIONS

Levera RTU (Levetiracetam in Sodium Chloride Injection) is an antiepileptic drug indicated as adjunctive therapy when oral administration is temporarily not feasible in adults (16 years and older) with the following types of seizures:

- Partial onset seizures
- Myoclonic seizures in patients with juvenile myoclonic epilepsy
- Primary generalized tonic-clonic seizures in adults with idiopathic generalized epilepsy

DOSAGE AND ADMINISTRATION

General Information

- For intravenous use only
- Do not dilute prior to its use
- Administer dose-specific 100 mL infusion bottle intravenously over 15-minutes
- Levetiracetam can be initiated with either intravenous or oral administration

Initial Exposure to Levetiracetam

Partial Onset Seizures: Initial dose is 1000 mg/day, divided as 500 mg twice daily. Increase dose as needed and tolerated in increments of 1000 mg/day, every 2 weeks to a maximum recommended daily dose of 3000 mg.

Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy: Initial dose is 1000 mg/day, divided as 500 mg twice daily. Increase dose 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: Initial dose is 1000 mg/day, divided as 500 mg twice daily. Increase dose 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: Initial total daily intravenous levetiracetam dose regimen should be equivalent to total daily dose and frequency of oral levetiracetam.

Switching to Oral Dosing: Give equivalent daily dose and frequency of oral as intravenous levetiracetam.

Adult patients with Renal Impairment: Levetiracetam dosing is individualised according to the patient's renal function status (as indicated by creatinine clearance, CLcr). Recommended dosing and dose adjustments should be done according to the table below (Table 1).

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 h
Mild	50 – 80	500 to 1,000	Every 12 h
Moderate	30 – 50	250 to 750	Every 12 h
Severe	< 30	250 to 500	Every 12 h
ESRD patients using dialysis	----	500 to 1,000	(1)Every 24 h
(1) 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 infusion bottle 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 infusion bottle must be discarded. Do not store or reuse.

Compatibility with Other Antiepileptic Drugs: Levera RTU (Levetiracetam in Sodium Chloride Injection) is found to be physically compatible and chemically stable for at least 24 hours when mixed with lorazepam, diazepam, and valproate sodium and stored at controlled room temperature 15° to 30°C (59° to 86°F).

There are no data to support the physical compatibility of levetiracetam injection with antiepileptic drugs that are not listed above.

USE IN SPECIFIC POPULATIONS

Pregnancy

In animal studies, levetiracetam produced evidence of developmental toxicity at doses similar to or greater than human therapeutic doses.

There are no adequate and well-controlled studies in pregnant women. Levetiracetam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

US FDA Pregnancy Category C

Labor and Delivery

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

Nursing Mothers

Levetiracetam is excreted in breast 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.

Pediatric Use

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

Geriatric Use

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. The dosage should be reduced in patients with impaired renal function receiving levetiracetam and supplemental doses should be given to patients after dialysis.

CONTRAINDICATIONS

None.

WARNINGS

Neuropsychiatric Adverse Events

Levetiracetam use in adults and children has been associated with the occurrence of central nervous system adverse events that can be classified into the following categories: 1) somnolence and fatigue, 2) coordination difficulties, and 3) behavioral abnormalities.

Some levetiracetam-treated patients may experience somnolence and asthenia. In controlled trials of adult patients with partial onset seizures, 14.8% and 14.7% of levetiracetam-treated patients reported somnolence and asthenia, respectively, compared to placebo-treated patients (8.4% and 9.1%).

Some patients may experience coordination difficulties, (reported as ataxia, abnormal gait, or incoordination). Somnolence, asthenia and coordination difficulties occurred most frequently within the first four weeks of treatment.

Levetiracetam-treated epilepsy patients have also experienced psychosis, hallucinations, psychotic depression and other behavioral symptoms (reported as aggressive behaviour, agitation, hostility, anxiety, apathy, emotional lability, depersonalization, depression, etc.). In addition, some of the patients treated with levetiracetam attempted suicide.

Withdrawal Seizures

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

PRECAUTIONS

Hematologic Abnormalities

In clinical trials, a few levetiracetam treated adult patients showed minor, but statistically significant, decreases in total mean RBC count (0.03 X $10^9/mm^2$), mean hemoglobin (0.09 g/dL), and mean hematocrit (0.38%).

A few levetiracetam-treated pediatric patients with partial seizures showed minor, but statistically significant, decrease in WBC and neutrophil counts.

Hepatic Abnormalities

There were no meaningful changes in mean liver function tests (LFT) in controlled trials in adult or pediatric patients; lesser LFT abnormalities were similar in drug and placebo treated patients in controlled trials (1.4%).

Laboratory Tests

Most laboratory tests are not significantly altered.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Studies in the rats and mice with levetiracetam doses corresponding to up to 6 times the maximum recommended daily human dose have not revealed any evidence of carcinogenicity.

Mutagenesis

Levetiracetam was shown to be devoid of significant mutagenic potential in routinely employed mutagenicity studies.

Impairment of Fertility

No adverse effects on male or female fertility or reproductive performance were observed in rats at doses up to 1800 mg/kg/day (approximately 6 times the maximum recommended human dose on a mg/m^2 or exposure basis).

DRUG INTERACTIONS

Pharmacokinetic Interactions

Levetiracetam does not affect the concentrations of carbamazepine, clobazam, clonazepam, diazepam, gabapentin, lamotrigine, phenytoin, phenobarbital, primidone, valproic acid, vigabatrin, and ethosuximide.

Conversely, phenytoin, methsuximide, carbamazepine, and oxcarbazepine have been shown to lower levetiracetam concentrations, while valproic acid minimally affected them.

Levetiracetam and other AEDs that do not induce cytochrome P450 enzymes are not expected to interact with oral contraceptives.

Pharmacodynamic Interactions

Negative pharmacodynamic interactions have been reported with carbamazepine and topiramate. Some anecdotal evidence suggests that add-on use of levetiracetam could possibly result in increased symptomatic carbamazepine or topiramate neurotoxicity.

ADVERSE REACTIONS

Undesirable effects that resulted from intravenous use of levetiracetam are similar to those associated with oral use of the drug. The most frequently reported adverse reactions were dizziness, somnolence, headache and postural dizziness. Since there was limited exposure for levetiracetam intravenous use and since oral and intravenous formulations are bioequivalent, the safety information of levetiracetam intravenous will rely on levetiracetam oral use.

Pooled safety data from clinical studies conducted with levetiracetam oral formulations in adult patients with partial onset seizures showed that 46.4% of the patients in the levetiracetam group and 42.2% of the patients in the placebo group experienced undesirable effects. Serious undesirable effects were experienced in 2.4% of the patients in the levetiracetam and 2.0% of the patients in the placebo groups. The most commonly reported undesirable effects were somnolence, asthenia and dizziness. In the pooled safety analysis, there was no clear dose-response relationship but incidence and severity of the central nervous system related undesirable effects decreased over time.

In monotherapy 49.8 % of the subjects experienced at least one drug-related undesirable effect. The most frequently reported undesirable effects were fatigue and somnolence.

A study conducted in paediatric patients (4 to 16 years) with partial onset seizures showed that 55.4 % of the patients in the levetiracetam group and 40.2 % of the patients in the placebo group experienced undesirable effects. Serious undesirable effects were experienced in 0% of the patients in the levetiracetam group and 1.0% of the patients in the placebo group. The most commonly reported undesirable effects were somnolence, hostility, nervousness, emotional lability, agitation, anorexia, asthenia and headache in the paediatric population. Safety results in paediatric patients were consistent with the safety profile of levetiracetam in adults except for behavioural and psychiatric adverse events which were more common in children than in adults (38.6% versus 18.6%). However, the relative risk was similar in children as compared to adults.

Undesirable effects reported in clinical studies (adults and children) or from post-marketing experience are listed in the following table per System Organ Class and per frequency. For clinical trials, the frequency is defined as follows: very common (≥1/10); common (≥1/100,<1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports. Data from post-marketing experience are insufficient to support an estimate of their incidence in the population to be treated.

- General disorders and administration site conditions
  Very common: asthenia/fatigue
- Nervous system disorders
  Very common: somnolence
  Common: amnesia, ataxia, convulsion, dizziness, headache, hyperkinesia, tremor, balance disorder, disturbance in attention, memory impairment.
  Post-marketing experience: paresthesia
- Psychiatric disorders
  Common: agitation, depression, emotional lability/mood swings, hostility/aggression, insomnia, nervousness/irritability, personality disorders, thinking abnormal
  Post-marketing experience: abnormal behaviour, anger, anxiety, confusion, hallucination, psychotic disorder, suicide, suicide attempt and suicidal ideation
- Gastrointestinal disorders
  Common: abdominal pain, diarrhoea, dyspepsia, nausea, vomiting
  Post-marketing experience: pancreatitis
- Hepatobiliary disorders:
  Post-marketing experience: hepatic failure, hepatitis, liver function test abnormal
- Metabolism and nutrition disorders
  Common: anorexia, weight increase.
  (The risk of anorexia is higher when topiramate is coadministered with levetiracetam).
  Post-marketing experience: weight loss
- Ear and labyrinth disorders
  Common: vertigo
- Eye disorders
  Common: diplopia, vision blurred
- Musculoskeletal and connective tissue disorders
  Common: myalgia
- Injury, poisoning and procedural complications
  Common: accidental injury
- Infections and infestations
  Common: infection, nasopharyngitis
- Respiratory, thoracic and mediastinal disorders
  Common: cough increased
- Skin and subcutaneous tissue disorders
  Common: rash, eczema, pruritus
  Post-marketing experience: alopecia: in several cases, recovery was observed when levetiracetam was discontinued.
- Blood and lymphatic system disorders

Common: thrombocytopenia

Post-marketing experience: leukopenia, neutropenia, pancytopenia (with bone marrow suppression identified in some of the cases)

OVERDOSAGE

Symptoms:

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.

PHARMACODYNAMIC PROPERTIES

Levetiracetam has demonstrated anticonvulsant effect in several rat models of seizures. It is particularly active in rat seizure models with kindling-induced seizures. On the contrary, it is not active in the maximal electroshock-induced seizures and chemoconvulsant-induced clonic seizures in animal models.

The antiepileptic effect of levetiracetam is probably accounted by (1) its ability to prevent intracellular calcium (Ca^{2+}) overload secondary to blocking the neuronal N-type calcium channel, and (2) negative modulation of neurotransmitter release consequent to its binding to synaptic vesicle protein SV2A at presynaptic sites in the brain. It also seems to indirectly promote inhibitory neurotransmission by gamma-amino butyric acid and glycine.

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.

The pharmacokinetics of levetiracetam have been studied in healthy adult subjects, adults and pediatric patients with epilepsy, elderly subjects and subjects with renal and hepatic impairment.

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 signifi cant 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 impaired renal function.

Special 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

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

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 >80mL/min). Approximately 50% of the pool of levetiracetam in the body is removed during a standard 4 hour hemodialysis procedure.

Dosage should be reduced in patients with impaired renal function receiving levetiracetam, and supplemental doses should be given to patients after dialysis.

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.

INCOMPATIBILITIES

Levera RTU (Levetiracetam in Sodium Chloride Injection) is found to be physically compatible and chemically stable for at least 24 hours when mixed with lorazepam, diazepam, and valproate sodium and stored at controlled room temperature 15° to 30°C (59° to 86°F).

SHELF-LIFE

Two years from the date of manufacturing.

PACKAGING INFORMATION

- Levera RTU 1500 – Levetiracetam in 0.54% Sodium Chloride Injection (1500 mg/100 mL Infusion Bottle)
- Levera RTU 1000 - Levetiracetam in 0.75% Sodium Chloride Injection (1000 mg/100 mL Infusion Bottle)
- Levera RTU 500 – Levetiracetam in 0.82% Sodium Chloride Injection (500 mg/100 mL Infusion Bottle)

STORAGE AND HANDLING INSTRUCTIONS

Store at 20°C to 25°C (68°F to 77°F).

Keep all medicines away from the sight and reach of children.

Manufactured by :

INTAS

INTAS PHARMACEUTICALS LTD.

Plot No. 457-458, Village - Matoda,
Bavla Road, Ta. Sanand, Dist. Ahmedabad

Marketed by :

Intas Pharmaceuticals Ltd.,
Chinubhai Centre, Off Nehru Bridge, Ashram Road,
Ahmedabad - 380 009. India

INTAS	AW No./AW Code :			
	Size :	134 x 234 (mm)		
Pantone No :	Black			
Date :	18/05/2018			
Checked by :	Packaging Dev.	Packaging Dev.	C.Q.A.	Approved by C.Q.A.
Signature & Date				