PRESCRIBING INFORMATION

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

LEVERA

COMPOSITION

LEVERA 250 / 500 / 750 / 1000
Each film-coated tablet contains Levetiracetam 250mg / 500mg / 750mg / 1000mg

LEVERA ORAL SOLUTION
Each mL solution contains Levetiracetam 100mg

LEVERA XR 500 / 750 / 1000

Each film coated tablet contains Levetiracetam Sustained-Release Oral Tablets 500mg, 750mg, and 1000mg)

LEVERA RTU 500
Levetiracetam in 0.82% Sodium Chloride Injection, 500 mg/100 mL Infusion Bottle
Each 100 mL contains: Levetiracetam IP 500 mg

LEVERA RTU 1000
Levetiracetam in 0.75% Sodium Chloride Injection, 1000 mg/100 mL Infusion Bottle
Each 100 mL contains: Levetiracetam IP 1000 mg

LEVERA RTU 1500
Levetiracetam in 0.54% Sodium Chloride Injection, 1500 mg/100 mL Infusion Bottle
Each 100 mL contains: Levetiracetam IP 1500 mg

LEVERA DT 250 / 500

Each Dispersible Tablets contains Levetiracetam 250 mg / 500 mg

DESCRIPTION

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).

CLINICAL PHARMACOLOGY

Mechanism of Action

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.

Pharmacokinetics

Absorption and Distribution

Levetiracetam is rapidly and almost completely (>95%) absorbed following oral ingestion with time to peak plasma concentration (T_{max}) occurring at 1.3-5.2 h. Food does not affect the extent of absorption of levetiracetam but it decreases the peak plasma concentration (C_{max}) by 20% and delays T_{max} by 1.5 h. 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. The mean half-life in serum is 6-13.3 h.

Bioavailability of LEVERA XR tablets is similar to that of the LEVERA immediate-release tablets. The pharmacokinetics (AUC and Cmax) are dose proportional after single dose administration of 1000 mg sustained-release levetiracetam. Mean plasma elimination half-life of sustained-release levetiracetam is approximately 9 hours

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.

Levetiracetam readily enters the cerebrospinal fluid compartment with a T_{max} of 3-7.3 h. 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, Excretion and Elimination

In humans levetiracetam is minimally metabolised and almost completely excreted in the urine. About 34% of the administered dose is metabolised (not involving hepatic cytochrome P450 system) and 66% is recovered unchanged in the urine. Levetiracetam is rapidly cleared by the kidneys proportional to creatinine clearance, with >90% of the drug being excreted within 48 h.

Metabolism occurs mainly in blood, where an amidase hydrolyses levetiracetam to an inactive metabolite.

Overall, no significant differences in pharmacokinetics between sexes or races have been reported, although some special populations require extra care.

Special Populations

Pediatric Patients: In children, renal clearance of levetiracetam is higher and dosage should be increased to approximately 130% of the adult dose on a per kg of body weight basis.

Elderly: Elderly people often show a reduction in renal clearance and dosage should be lowered accordingly. Likewise, in patients showing renal impairment or suffering from hepatorenal syndrome, dosage reduction should be considered.

INDICATIONS

LEVERA TABLETs, LEVERA DT and ORAL SOLUTION are intended for adjunctive therapy of the following seizure disorders:

- Partial onset seizures in patients one month of age and older with epilepsy.
- Myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy.
- Primary generalized tonic-clonic seizures in patients 6 years of age and older with idiopathic generalized epilepsy.

LEVERA TABLETs are also intended for monotherapy of the following:
Partial-onset seizures with or without secondary generalisation in patients age 16 years and older.

LEVERA XR is indicated as adjunctive therapy in the treatment of partial onset seizures in epilepsy patients 16 years of age or older.

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

LEVERA is taken orally with or without food.

LEVERA TABLETS should be swallowed whole. Tablets should not be chewed or crushed.
Use **LEVERA ORAL SOLUTION** for pediatric patients with body weight ≤ 20 kg.
For pediatric patients, use weight-based dosing for the oral solution.

Partial Onset Seizures

- 1 Month to <6 Months: Start with 7 mg/kg twice daily, increase in increments of 7 mg/kg twice daily every 2 weeks to recommended dose of 21 mg/kg twice daily.
- 6 Months to <4 Years: Start with 10 mg/kg twice daily, increase in increments of 10 mg/kg twice daily every 2 weeks to recommended dose of 25 mg/kg twice daily.
- 4 Years to <16 Years: Start with 10 mg/kg twice daily, increase in increments of 10 mg/kg twice daily every 2 weeks to recommended dose of 30 mg/kg twice daily.
- Adults 16 Years and Older: Start with 500 mg twice daily, increase as needed and tolerated in increments of 500 mg twice daily every 2 weeks to a maximum recommended dose of 1500 mg twice daily.

Myoclonic Seizures in Adults and Pediatric Patients 12 Years and Older

- Start with 500 mg twice daily, increase by 500 mg twice daily every 2 weeks to recommended dose of 1500 mg twice daily.

Primary Generalized Tonic-Clonic Seizures

- 6 Years to < 16 Years: Start with 10 mg/kg twice daily, increase in increments of 10 mg/kg twice daily every 2 weeks to recommended dose of 30 mg/kg twice daily.
- Adults 16 Years and Older: Start with 500 mg twice daily, increase by 500 mg twice daily every 2 weeks to recommended dose of 1500 mg twice daily.

Adult Patients with Impaired Renal Function

- Dose adjustment is recommended, based on the patient's estimated creatinine clearance (CLcr) (Table 2). CLcr in mL/min may be estimated from serum creatinine (mg/dL) determination using the following formula:

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

Then CLcr is adjusted for body surface area (BSA) as follows:

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

Table 2: Dosing adjustment regimen for adult patients with impaired renal function

Group	Creatinine Clearance (mL/min)	Dosage (mg)	Frequency
Normal	> 80	500 to 1500	Every 12 h
Mild	50 – 80	500 to 1000	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 1000	Every 24 h*
* Following dialysis, a 250 to 500 mg supplemental dose is recommended.			

LEVERA XR

For Patients Aged ≥16 Years

Treatment should be initiated with a dose of 1000 mg once daily. The daily dosage may be adjusted in increments of 1000 mg every 2 weeks to a maximum recommended daily dose of 3000 mg.

LEVERA XR can be taken with or without food. Tablets are to be swallowed whole with water and not to be crushed, split, or chewed.

Adult Patients with Impaired Renal Function

Dosing of LEVERA XR must be individualized according to the patient's renal function status. Recommended doses and adjustment for dose for adults are shown in Table 3. 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:

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

Table 3: LEVERA XR dosing adjustment regimen for adult patients with impaired renal function

Group	**Creatinine Clearance (mL/min/1.73m^2)**	**Dosage (mg)**	**Frequency**
Normal	> 80	1000 to 3000	Every 24 h
Mild	50 – 80	1000 to 2000	Every 24 h
Moderate	30 – 50	500 to 1500	Every 24 h
Severe	< 30	500 to 1000	Every 24 h

LEVERA RTU

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 4).

Table 4: 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

CONTRAINDICATIONS
LEVERA should not be administered to patients who have previously exhibited hypersensitivity to levetiracetam or any of the inactive ingredients in levetiracetam tablets.

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 inco-ordination). 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 ($0.03 \times 10^6/mm^2$), 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.

Use in Patients with Impaired Renal Function
Caution should be taken in dosing patients with moderate and severe renal impairment and patients undergoing hemodialysis. Dosage should be reduced in patients with impaired renal function receiving levetiracetam and supplemental doses should be given to patients after dialysis.

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).

Pregnancy
Pregnancy Category C
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.

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 4 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.

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

The pattern of adverse events reported in clinical trials varied somewhat on the basis of seizure type and age group of the patients. Overall, frequently reported (>10% incidence) adverse events (in add-on therapy studies and monotherapy studies taken together) included somnolence, asthenia, infection and dizziness.

Common adverse events (>1 – 10% incidence in clinical studies) include the following:

Nervous system disorders: dizziness, headache, hyperactivity, ataxia (impaired coordinated movements), tremor, amnesia, loss of concentration, forgetfulness

Psychiatric disorders: agitation, depression, emotional instability/mood swings, hostility or aggression, insomnia, nervousness or irritability, behavioral problems, slow thinking

Digestive disorders: abdominal pain, nausea, dyspepsia, diarrhoea, vomiting

Nutrition disorders: anorexia, weight increase

Ear and labyrinth disorders: vertigo

Eye disorders: diplopia, blurred vision

Musculoskeletal and connective tissue disorders: myalgia

Skin disorders: rash; eczema, pruritus

Blood disorders: decreased number of blood platelets

OVERDOSAGE

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans

The highest known dose of levetiracetam received in the clinical development program was 6000 mg/day. Other than drowsiness, there were no adverse events in the few known cases of overdose.

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 clinical status of patient.

Levera RTU: 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).

Hemodialysis
Standard hemodialysis procedures result in significant clearance of levetiracetam (approximately 50% in 4 hours) and should be considered in cases of overdose.

STORAGE
Store in a cool and dry place at 15-30°C.
Keep all medicines away from the sight and reach of children.

PRESENTATION
TABLET LEVERA 250: Strip of 15 Tabs
TABLET LEVERA 500: Strip of 15 Tabs
TABLET LEVERA 750: Strip of 10 Tabs
TABLET LEVERA 1000: Strip of 10 Tabs
LEVERAL ORAL SLUTION: 100 ML and 200 ML
LEVERA DT 250: Strip of 10 Tabs
LEVERA DT 500: Strip of 10 Tabs
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)

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