Klevra®

كليورا

Levetiracetam USP

PHARMACEUTICAL FORM AND STRENGTHS

Klevra® Oral Solution:
Each 5ml contains 500 mg Levetiracetam USP

Klevra® 250 mg tablet:
Each film-coated tablet contains 250 mg Levetiracetam USP

Klevra® 500 mg tablet:
Each film-coated tablet contains 500 mg Levetiracetam USP
(USP Specs.)

PHARMACOTHERAPEUTIC GROUP
Antiepileptics

THERAPEUTIC INDICATIONS
Levetiracetam is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy.

Levetiracetam is indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults and children from 4 years of age with epilepsy.

Levetiracetam is indicated in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.

Levetiracetam is indicated in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy.

POSOLOGY AND METHOD OF ADMINISTRATION
The film-coated tablets must be taken orally, swallowed with a sufficient quantity of liquid and may be taken with or without food. The daily dose is administered in two equally divided doses.

• Monotherapy

Adults and adolescents from 16 years of age: The recommended starting dose is 250 mg twice daily which should be increased to an initial therapeutic dose of 500 mg twice daily after two weeks. The dose can be further increased by 250 mg twice daily every two weeks depending upon the clinical response. The maximum dose is 1500 mg twice daily.

• Add-on therapy

Adults (> 18 years) and adolescents (12 to 17 years) weighing 50 kg or more: The initial therapeutic dose is 500 mg twice daily. This dose can be started on the first day of treatment. Depending upon the clinical response and tolerability, the daily dose can be increased up to 3,000 mg daily. Dose changes can be made in 500 mg twice daily increases or decreases every two to four weeks.

Elderly (65 years and older): Adjustment of the dose is recommended in elderly patients with compromised renal function (see "Patients with renal impairment" below)

Children aged 4 to 11 years and adolescents (12 to 17 years) weighing less than 50 kg: The initial therapeutic dose is 10 mg/kg twice daily. Depending upon the clinical response and tolerability, the dose can be increased up to 30 mg/kg twice daily. Dose changes should not exceed, increases or decreases of 10 mg/kg twice daily every two weeks. The lowest effective dose should be used. Dosage in children 50 kg or greater is the same as in adults. The physician should prescribe the most appropriate pharmaceutical form and strength according to weight and dose.

Dosage recommendations for children and adolescents

Weight	Starting dose	Maximum dose
15 kg	150 mg twice daily	450 mg twice daily
20 kg	200 mg twice daily	600 mg twice daily
25 kg	250 mg twice daily	750 mg twice daily
From 50 kg	500 mg twice daily	1500 mg twice daily

Infants and children less than 4 years: Levetiracetam is not recommended for use in children below 4 years of age due to insufficient data on safety and efficacy.

Patients with renal impairment: The daily dose must be individualised according to renal function.
For adult patients, refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in ml/min is needed. The CLcr in ml/min may be estimated from serum creatinine (mg/dl) determination using the following formula:

$$CLcr = \frac{(140\text{-age (years)}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} \quad (\times 0.85 \text{ for women})$$

Dosing adjustment for adult patients with impaired

Group	Creatinine Clearance (ml/min/1.73m^2)	Dosage and Frequency
Normal	>80	500 to 1,500 mg twice daily
Mild	50-79	500 to 1,000 mg twice daily
Moderate	30-49	250 to 750 mg twice daily
Severe	<30	250 to 500 mg twice daily
End-stage renal disease patients Undergoing dialysis		500 to 1,000 mg once daily

For children with renal impairment, levetiracetam dose needs to be adjusted based on the renal function as levetiracetam clearance is related to renal function. This recommendation is based on a study in adult renally impaired patients.

Patients with hepatic impairment: No dose adjustment is needed in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the creatinine clearance may underestimate the renal insufficiency. Therefore a 50 % reduction of the daily maintenance dose is recommended when the creatinine clearance is < 70 ml/min.

CONTRAINDICATIONS
Hypersensitivity to levetiracetam or other pyrrolidone derivatives or any of the excipients.

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE
In accordance with current clinical practice, if Levetiracetam has to be discontinued it is recommended to withdraw it gradually (e.g. 500 mg twice daily decrements every two to four weeks). In a study reflecting clinical practice, the concomitant antiepileptic medication could be withdrawn in a limited number of patients who responded to levetiracetam adjunctive therapy (36 patients out of 69). An increase in seizure frequency of more than 25 % has been reported in 14 % and 26 % of the levetiracetam and placebo treated patients, respectively. The administration of Levetiracetam to patients with renal impairment may require dose adaptation. In patients with severely impaired hepatic function, assessment of renal function is recommended before dose selection.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Levetiracetam did-not influence the serum concentrations of existing antiepileptic medicinal products (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these antiepileptic medicinal products did not influence the pharmacokinetics of Levetiracetam.
Probenecid (500 mg four times daily), a renal tubular secretion blocking agent, has been shown to inhibit the renal clearance of the primary metabolite but not of levetiracetam. . Nevertheless, the concentration of this metabolite remains low. It is expected that other drugs excreted by active tubular, secretion could also reduce the renal clearance of the metabolite. The effect of levetiracetam on probenecid was not studied and the effect of levetiracetam on other actively secreted drugs, e.g. NSAIDs, sulphonamides and methotrexate is unknown.
Levetiracetam 500 mg twice daily did not influence the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel); endocrine parameters (luteinizing hormone and progesterone) were not modified. Levetiracetam 500 mg QID did not influence the pharmacokinetics of digoxin and warfarin; prothrombin times were not modified. Coadministration with digoxin, oral contraceptives and warfarin did not influence the pharmacokinetics of levetiracetam.
No data on the influence of antacids on the absorption of levetiracetam are available. The extent of absorption of levetiracetam was not altered by food, but the rate of absorption was slightly reduced. No data on the interaction of levetiracetam with alcohol are available.

PREGNANCY AND LACTATION
There are no adequate data from the use of Levetiracetam in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for human is unknown.
Levetiracetam should not be used during pregnancy unless clearly necessary. Discontinuation of antiepileptic treatments may result in disease worsening, harmful to the mother and the fetus. Levetiracetam is excreted in human breast milk. Therefore, breast-feeding is not recommended.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
No studies on the effects on the ability to drive and use machines have been performed. Due to possible different individual sensitivity, some patients might experience, at the beginning of treatment or following a dose increase, somnolence or other central nervous system related symptoms. Therefore, caution is recommended in those patients when performing skilled tasks, e.g. driving vehicles or operating machinery.

UNDESIRABLE EFFECTS
Pooled safety data from clinical studies showed that 46.4 % and 42.2 % of the patients experienced undesirable effects in the Levetiracetam and placebo groups, respectively, and that 2.4 % and 2.0 % of the patients experienced serious undesirable effects in the Levetiracetam and placebo groups, respectively. 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.

Undesirable effects reported in clinical studies are mention below per System Organ Class and per frequency. For clinical trials, the frequency is defined as follows: very common: > 10 %; common: > 1 -10 %; uncommon: > 0.1 % - 1 %; rare: 0.01 % - 0.1 %; very rare: < 0.01 %, including isolated reports.

General disorders and administration site conditions
Very common: asthenia
Nervous system disorders
Very common: somnolence
Common: amnesia, ataxia, convulsion, dizziness, headache, tremor Psychiatric disorders
Common: depression, emotional lability, hostility, insomnia, nervousness.
Uncommon: abnormal behaviour, aggression, anger, anxiety, confusion, hallucination, irritability, psychotic disorder, suicide attempt and suicidal ideation
Gastrointestinal disorders
Common: diarrhoea, dyspepsia, nausea

Metabolism and nutrition disorders
Common: anorexia

Ear and labyrinth disorders
Common: vertigo

Eye disorders
Common: diplopia Injury, poisoning and procedural complications
Common: accidental injury

Skin and subcutaneous tissue disorders
Common: rash, alopecia

Blood and lymphatic system disorders
Post-marketing experience: leukopenia, neutropenia, pancytopenia, thrombocytopenia

OVERDOSE
Symptoms
Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with Levetiracetam overdoses.

Management of overdose
After an acute overdose, the stomach may be emptied by gastric lavage or by induction of emesis. There is no specific antidote for levetiracetam. Treatment of an overdose will be symptomatic and may include haemodialysis. The dialyser extraction efficiency is 60 % for levetiracetam and 74 % for the primary metabolite.

Pharmacodynamic effects
Levetiracetam induces seizure protection in a broad range of animal models of partial and primary generalised seizures without having a pro-convulsant effect. The primary metabolite is inactive.

In man, an activity in both partial and generalised epilepsy conditions (epileptiform discharge/photoparoxysmal response) has confirmed the broad spectrum pharmacological profile of levetiracetam.

PHARMACOKINETIC PROPERTIES

Adults and adolescents

Absorption: Levetiracetam is rapidly absorbed after oral administration. Oral absolute bioavailability is close to 100%. Peak plasma concentrations (C_{max}) are achieved in 78 minutes after dosing. Steady-state is achieved after two days of a twice daily administration schedule. The extent of absorption is dose-independent and is not altered by food.

Distribution: No tissue distribution data are available in humans. Neither levetiracetam nor its primary metabolite are significantly bound to plasma proteins (< 10%). The volume of distribution of levetiracetam is approximately 0.5 to 0.7 l/kg, a value close to the total body water volume.

Biotransformation: Levetiracetam is not extensively metabolised in humans. The major metabolic pathway (24 % of the dose) is an enzymatic hydrolysis of the acetamide group. Production of the primary metabolite is not supported by liver cytochrome P450 isoforms. Hydrolysis of the acetamide group was measurable in a large number of tissues including blood cells.
In vitro, levetiracetam and its primary metabolite have been shown not to inhibit the major human liver cytochrome P450 isoforms (CYP3A4, 2A6, 2C8/9/10, 2C19, 2D6, 2E1 and 1A2). glucuronyl transferase (UGT1*6, UGT1M and UGT [PL6.2]) and epoxide hydroxylase activities. In addition, levetiracetam does not affect the in vitro glucuronidation of valproic acid.

In human hepatocytes in culture, levetiracetam did not cause enzyme induction. Therefore, the interaction of Levetiracetam with other substances, or vice versa, is unlikely.

Elimination: The plasma half-life in adults was 7±1 hours and did not vary either with dose, route of administration or repeated administration. The mean total body clearance was 0.96 ml/min/kg. The major route of excretion was via urine, accounting for a mean 95 % of the dose (approximately 93 % of the dose was excreted within 48 hours). Excretion via faeces accounted for only 0.3 % of the dose. The cumulative urinary excretion of levetiracetam and its primary metabolite accounted for 66 % and 24 % of the dose, respectively during the first 48 hours.

The renal clearance of levetiracetam and metabolite is 0.6 and 4.2 ml/min/kg respectively indicating that levetiracetam is excreted by glomerular filtration with subsequent tubular reabsorption and that the primary metabolite is also excreted by active tubular secretion in addition to glomerular filtration. Levetiracetam elimination is co-related to creatinine clearance.

Elderly: In the elderly, the half-life is increased by about 40 % (10 to 11 hours). This is related to the decrease in renal function in this population.

Children (4 to 12 years): Following single oral dose administration (20 mg/kg) to epileptic children (6 to 12 years), the half-life of levetiracetam was 6.0 hours. The apparent body weight adjusted clearance was approximately 30 % higher than in epileptic adults.

Following repeated oral dose administration (20 to 60 mg/kg/day) to epileptic children (4 to 12 years), levetiracetam was rapidly absorbed. Peak plasma concentration was observed 0.5 to 1.0 hour after dosing. The elimination half-life was approximately 5 hours. The apparent body clearance was 1.1 ml/min/kg.

Infants and children (1 month to 4 years): Following single dose administration (20 mg/kg) orally solution to epileptic children (1 month to 4 years), levetiracetam was rapidly absorbed and peak plasma concentrations were observed approximately 1 hour after dosing. The pharmacokinetic results indicated lhat 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).

PRESENTATION

Klevra® 250mg tablet: 3x10 film coated tablets
Klevra® 500mg tablet: 3x10 film coated tablets
Klevra® Oral Solution: 60ml Bottle with dropper and spoon

STORAGE CONDITIONS

Store below 30ºC.
Protect from heat, light and moisture .
Keep all medicines out of the reach of children.

ہدایات:

صرف رجسٹرڈ ڈاکٹر کے نُسخہ پر ہی فروخت کی جائے۔
روشنی اور نمی سے محفوظ ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
ڈاکٹر کی ہدایت کے مُطابق استعمال کریں۔
تمام دوائیں بچوں کی پہنچ سے دُور رکھیں۔

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