FITZLOC®
(Levetiracetam)

فٹزلوک

QUALITATIVE AND QUANTITATIVE COMPOSITION
FITZLOC 250 mg Tablets
Each film-coated tablet contains:
Levetiracetam (USP).....250 mg

FITZLOC 500 mg Tablets
Each film-coated tablet contains:
Levetiracetam (USP).....500 mg

DESCRIPTION
FITZLOC contains Levetiracetam which is a single enantiomer. Its chemical name 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.

CLINICAL INFORMATION
Indications
FITZLOC (Levetiracetam) is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy.
FITZLOC (Levetiracetam) is an antiepileptic drug indicated for adjunctive therapy in the treatment of:
• 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.

Dosage and Administration
Partial Onset Seizures
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 (500 mg twice a day adding every 2 weeks) to a maximum recommended daily dose of 3000 mg/day.
Pediatric Patients: Ages 4 To <16 Years
For pediatric patients weighing 20 to 40 kg, treatment should be initiated with a daily dose of 500 mg given as twice daily dosing (250 mg twice daily). The daily dose should be increased every 2 weeks by increments of 500 mg to a maximum recommended daily dose of 1500 mg (750 mg twice daily).
For pediatric patients weighing more than 40 kg, treatment should be initiated with a daily dose of 1000 mg/day given as twice daily dosing (500 mg twice daily). The daily dose should be increased every 2 weeks by increments of 1000 mg/day to a maximum recommended daily dose of 3000 mg/day (1500 mg twice daily).
Myoclonic Seizures in Patients 12 Years of Age and Older With Juvenile Myoclonic Epilepsy
Treatment should be initiated with a dose of 1000 mg/day, given as twice-daily dosing (500 mg twice daily). Dosage should be increased by 1000 mg/day every 2 weeks to the recommended daily dose of 3000 mg/day. Data regarding the effectiveness of doses lower than 3000 mg/day is not available.
Primary Generalized Tonic-Clonic Seizures
Adults 16 Years and Older
Treatment should be initiated with a dose of 1000 mg/day, given as twice-daily dosing (500 mg twice daily). Dosage should be increased by 1000 mg/day every 2 weeks to the recommended daily dose of 3000 mg/day.
Pediatric Patients Ages 6 to <16 Years
Treatment should be initiated with a daily dose of 20 mg/kg in 2 divided doses (10 mg/kg twice daily). 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 twice daily). FITZLOC (Levetiracetam) tablet is to be used in patients with body weight above 20kg.
Adult patients with impaired renal function
FITZLOC (Levetiracetam) dosing must be individualized according to the patient's renal function status. Recommended doses and adjustment for dose for adults >50kg are shown in the following table.

Group	Creatnine Clearance (mL/min/1.73m^2)	Dosage(mg)	Frequency
Normal	>80	500-1500	Every 12 hours
Mild	50-80	500-1000	Every 12 hours
Moderate	30-50	250-750	Every 12 hours
Severe	<30	250-500	Every 12 hours
ESRD patients using dialysis	----	500-1000	Every 24 hours

Recommended dosing adjustment for infants, children and adolescent patients weighing less than 50 kg with impaired renal function is shown in the following table:

Group	Group Creatinine clearance (ml/min/1.73m^2)	Dose and frequency[1]
		Infants 6 to 23 months, children and adolescents weighing less than 50 kg
Normal	≥ 80	10 to 30 mg/kg (0.10 to 0.30 ml/kg) twice daily
Mild	50-79	10 to 20 mg/kg (0.10 to 0.20 ml/kg) twice daily
Moderate	30-49	5 to 15 mg/kg (0.05 to 0.15 ml/kg) twice daily
Severe	< 30	5 to 10 mg/kg (0.05 to 0.10 ml/kg) twice daily
End-stage renal disease patients undergoing dialysis	--	10 to 20 mg/kg (0.10 to 0.20 ml/kg) once daily[1,2]

(1) A 15 mg/kg (0.15 ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.
(2) Following dialysis, a 5 to 10 mg/kg (0.05 to 0.10 ml/kg) supplemental dose is recommended.

Discontinuation of FITZLOC
Avoid abrupt withdrawal from FITZLOC (Levetiracetam) in order to reduce the risk of increased seizure frequency and status epilepticus.
Administration requirements
FITZLOC (Levetiracetam) is given orally with or without food. FITZLOC (Levetiracetam) dosing regimen depends on the indication, age group, dosage form and renal function.
FITZLOC (Levetiracetam) should be swallowed whole, should not be chewed or crushed.

Contraindications
Levetiracetam is contraindicated in patients with a hypersensitivity to levetiracetam. Reactions have included anaphylaxis and angioedema.

Warnings and Precautions
Behavioral Abnormalities
The psychiatric signs symptoms like behavioral abnormalities (aggression, agitation, anger, anxiety, apathy, depersonalization, depression, emotional lability, hostility, hyperkinesias, irritability, nervousness, neurosis, and personality disorder) should be monitored.
Suicidal Behavior
Patients treated with any antiepileptic drugs 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.
Signs and Symptoms of Somnolence and Fatigue
Patients should be monitored for signs and symptoms of somnolence and fatigue and advised not to drive or operate machinery until they have gained sufficient experience on Levetiracetam to gauge whether it adversely affects their ability to drive or operate machinery.
Anaphylaxis and Angioedema
Levetiracetam can cause anaphylaxis or angioedema after the first dose or at any time during treatment. Signs and symptoms include hypotension, hives, rash, respiratory distress, and swelling of the face, lip, mouth, eye, tongue, throat, and feet. Reactions maybe life threatening and may require 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.
Serious Dermatological Reactions
Serious dermatological reactions, including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), may occur in patients treated with Levetiracetam. The median time of onset is 14 to 17 days, but may also occur at least four months after initiation of treatment. Recurrence of the serious skin reactions following rechallenge with Levetiracetam is also known to occur. 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.
Withdrawal Seizures
Antiepileptic drugs, including levetiracetam, should be withdrawn gradually to minimize the potential of increased seizure frequency.
Geriatric Use 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. Dose adjustment is recommended for patients with impaired renal function and supplemental doses should be given to patients after dialysis.
Hematologic Abnormalities
Levetiracetam can cause hematologic abnormalities. Hematologic abnormalities may include decreases in White Blood Cell (WBC), neutrophil, and Red Blood Cell (RBC) counts; decreases in hemoglobin and hematocrit; and increases in eosinophil counts. Agranulocytosis, pancytopenia, and thrombocytopenia may also occur. A complete blood count is recommended in patients experiencing significant weakness, pyrexia, recurrent infections, or coagulation disorders.
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.

Interactions
Probenecid
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.
Methotrexate
Concomitant administration of Levetiracetam and Methotrexate may occur to decrease methotrexate clearance, resulting in increased/prolonged blood methotrexate concentration to potentially toxic levels. Blood Methotrexate and Levetiracetam levels should be carefully monitored in patients treated concomitantly with the two drugs.
Laxatives
Levetiracetam efficacy may be decreased when the osmotic laxative macrogol is concomitantly administered with oral levetiracetam. Therefore, macrogol should not be taken orally for one hour before and for one hour after taking levetiracetam.
Food
The extent of absorption of Levetiracetam is not altered by food, but the rate of absorption is slightly reduced.

Pregnancy and Breastfeeding

Category C

There is insufficient data available in pregnant women. Levetiracetam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Levetiracetam is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Effects on ability to drive and use machines

Levetiracetam has minor or moderate influence on the ability to drive and use machines. Due to possible different individual sensitivity, some patients might experience somnolence or other central nervous system related symptoms, especially at the beginning of treatment or following a dose increase. Therefore, caution is recommended in those patients when performing skilled tasks, *e.g.* driving vehicles or operating machinery. Patients are advised not to drive or use machines until it is established that their ability to perform such activities is not affected.

Levetiracetam may cause coordination difficulties reported as either ataxia, abnormal gait, or incoordination.

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.

Adverse Reactions

System Organ Classification	Frequency category			
	Very common	Common	Uncommon	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
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
Eye disorders			Diplopia, vision blurred	
Ear and labyrinth disorders		Vertigo		
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	

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

Overdose

The highest known dose of Levetiracetam is 6000 mg/day. Other than drowsiness, no adverse events may occur. Cases of somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma may be observed with Levetiracetam overdoses. There is no specific antidote for overdose with levetiracetam. If indicated, elimination of unabsorbed drug should be attempted by emesis or gastric lavage.

Hemodialysis

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

PHARMACOLOGICAL PROPERTIES

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

Mechanism of action

The precise mechanism(s) by which Levetiracetam exerts its antiepileptic effect is unknown. Levetiracetam inhibits burst firing without affecting normal neuronal excitability, suggesting that Levetiracetam may selectively prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity.

Pharmacokinetic properties

Absorption

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%. 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.

Distribution

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.

Metabolism

Levetiracetam is not extensively metabolized; about 25% of a dose is metabolized by hydroxylation to inactive metabolites.

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. Levetiracetam clearance is reduced in patients with impaired renal function.

PHARMACEUTICAL INFORMATION

Shelf life

2 Years.

Special Precautions for Storage

- Do not store above 30°C.
- Protect from light and moisture.
- Keep out of the reach of children.

ہدایات :

۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں۔
دوا کو روشنی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

Nature and contents of container

FITZLOC (Levetiracetam) 250 mg tablets are available in a blister pack of 10's (1x10's).
FITZLOC (Levetiracetam) 500 mg tablets are available in a blister pack of 10's (1x10's).

MANUFACTURED BY:

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REVISION DATE

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