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EPICETAM®

(Levetiracetam) Tablets & Syrup

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COMPOSITION:
Epicetam Tablet 250 mg:
Each film coated tablet contains:
Levetiracetam USP ..... 250 mg.

Product Specs.: USP

Epicetam Tablet 500 mg:
Each film coated tablet contains:
Levetiracetam USP ..... 500 mg.

Product Specs.: USP

Epicetam Tablet 750 mg:
Each film coated tablet contains:
Levetiracetam USP ..... 750 mg.

Product Specs.: USP

Epicetam Syrup 100 mg/ml:
Each ml contains:
Levetiracetam USP ..... 100 mg,

Product Specs.: USP

DESCRIPTION AND MODE OF ACTION:
Levetiracetam is an antiseizure (antiepileptic) drug. Its mechanism of action is unknown, but it inhibits the spread of seizure activity in the brain. The mechanism of action may relate to an interaction with a specific and stereo-selective binding site that is only found within the central nervous system.

PHARMACOKINETICS:
Adults and Adolescents:
Absorption: After oral administration, **Levetiracetam** is rapidly and almost completely absorbed and has an oral absolute bioavailability close to 100%. At 1.3 hours after dosing, peak plasma concentrations (C_{max}) are reached. After a twice daily administration schedule for two days, steady state is achieved. (C_{max}) peak concentrations are typically 31µg/mL following a single 1000 mg dose and 43µg/mL following repeated 1000mg b.i.d. dosing. Absorption is dose-independent. Absorption is not altered by food, but food slightly reduces the rate of absorption. **Levetiracetam** and its major metabolite are less than 10% bound to plasma proteins.
Distribution: Human tissue distribution data is not available.
Metabolism: The major metabolite produced from **Levetiracetam** is ucb L057 which results from an enzymatic hydrolysis of the acetamide group. This metabolite is pharmacologically inactive. Two minor metabolites were identified as the product of hydroxylation. There is no *in vivo* enantiomeric interconversion of **Levetiracetam** or its major metabolite.
Elimination: In adults, the plasma half-life was 7 ± 1 hour. The plasma half life did not vary with route of administration, repeated administration or dose. **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** elimination is correlated to creatinine clearance.
Special Population:
Elderly: The half-life is increased by 40% (10 to 11 hours) in elderly patients. This is attributed to the decrease in renal function in this patient population.
Children (4 to 12 years of age): In epileptic children (6 to 12 years of age) after a single dose of 20mg/kg, the half-life of **Levetiracetam** was 6.0 ± 1.1 hours. In epileptic children (6 to 12 years of age) the apparent body clearance was approximately 40% higher than in epileptic adults.
In epileptic children (4 to 12 years of age), **Levetiracetam** was rapidly absorbed following repeated administration of 20mg to 60mg/kg/day. Half an hour to one hour after dosing, peak plasma concentrations (C_{max}) were observed. Peak plasma concentrations and area under the curve were linear and dose proportional. The apparent body clearance was 1.1mL/min/kg and the elimination half-life was approximately 5 hours.
Renal impairment: **Levetiracetam** and its major metabolite ucb L057 apparent body clearances are correlated to the creatinine clearance. The **Levetiracetam** daily maintenance dose should be adjusted based on creatinine clearance in patients with moderate and severe renal impairment .
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
Hepatic impairment: In subjects with mild and moderate hepatic impairment, the clearance of **Levetiracetam** was not changed. In most subjects with severe hepatic impairment, clearance was reduced by more than 50% compared to normal subjects, due to concomitant renal impairment.

INDICATIONS:
Epicetam is indicated as adjunctive therapy in the treatment of partial onset seizures in adults and children 4 years of age and older with epilepsy.
Epicetam is indicated as adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents 12 years of age and older with juvenile myoclonic epilepsy.
Epicetam is indicated as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and children 6 years of age and older with idiopathic generalized epilepsy.

DOSAGE AND ADMINISTRATION:
Epicetam film coated tablets must be taken orally, with or without food, and swallowed with liquid. The daily dose is administered in two equal dose amounts i.e. 2 x 250 mg or 2 x 500 mg. Do not break the tablet to divide.
Adults (>18 years of age) and adolescents (aged 12-17 years of age) of 50kg or more:
The therapeutic dose is 500 mg twice daily as adjunctive therapy and this dose can be started on the first day of treatment. The daily dose can be increased up to 1500mg twice daily depending upon the clinical response and tolerance. Every two to four weeks, dose changes can be made in 500 mg twice daily increments or decrements. The maximum recommended daily dose is 3000 mg.
Elderly (65 years and older):
Adjustment of the dose is recommended in the elderly if they have compromised renal function.
Children (aged 6 to 11 years of age) and adolescents (aged 12-17 years of age) of less than 50kg:
The initial therapeutic dose is 10 mg/kg twice a day (i.e. if 25 kg then 250mg twice a day). The daily dose can be increased up to 60 mg/kg/daily (in two 30 mg/kg/doses), dependent on clinical response and tolerance. 10mg/kg twice daily dose changes can be made in increments or decrements every two weeks. The lowest effective dosage should be used.
For children over 50kg the dosage is the same as in adults.
According to weight and dose, the physician should describe the most appropriate strength.
Recommended dosing in children aged 6 years and older. Children 25kg:
Starting dose: 250 mg twice daily; Maximum dose: 750 mg twice daily.
Children from 50kg•
Starting dose: 500mg twice daily. Maximum dose: 1500 mg twice daily.
•The dosage in children and adolescents 50kg or greater is the same as adults.
Infants and children less than 6 years of age:
Epicetam tablets are not recommended for use in children less than 6 years of age:
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:
Total daily dose (mL/kg): $\frac{\text{Daily dose (mg/kg/day) x patient's weight (kg)}}{\text{100 mg/mL}}$

Patients with renal impairment: Dose adaptation may be required for the administration of **Levetiracetam** in patients with renal impairment. Dosage schedule based on renal function (Adults)

Group	Creatinine clearance (mL/min)	Frequency (daily)	Dosage (mg)
End-stage renal disease patients undergoing dialysis (A 750mg loading dose is recommended on the first day of treatment with Levetiracetam).	-	Once (following dailysis, a 250 to 500mg supplemental dose is recommended)	500 to 1,000
Severe	< 30	Twice	250 to 500
Moderate	30-49	Twice	250 to 750
Mild	50-79	Twice	500 to 1,000
Normal	> 80	Twice	500 to 1,500

In determining dosage, an estimate of the patient's creatinine clearance (Cl_{cr}) in mL/min is needed. The CL_{cr} in mL/min may be estimated from serum creatinine (mg/dL) using the following formula.

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

Using (BSA) body surface area the Cl_{cr} is adjusted using the following formulation:

$$Cl_{cr}\ (\text{mL/min/1.73m}^2) = \frac{[1.73 \times Cl_{cr}\ (\text{mL/min})}{\text{BSA subject}(\text{m}^2)}$$

For children with renal impairment, **Levetiracetam** clearance is related to renal function, therefore dosage needs to be adjusted based on renal function. This advice is recommended based on an adult impaired renal function study.
Patients with hepatic impairment: In patients with mild or moderate hepatic impairment no dose adjustment is needed. In patients with severe hepatic impairment when the creatinine clearance is < 70 mL/min, a 50% reduction of the daily maintenance dose is recommended.

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CONTRAINDICATIONS:
This product should not be administered to patients who have known hypersensitivity to **Levetiracetam** or any of the inactive ingredients in **Levetiracetam.**

WARNINGS AND PRECAUTIONS:
Withdrawal Seizures: **Levetiracetam** in accordance with current clinical practice should be withdrawn gradually if it has to be discontinued.
Suicidal Behavior & Ideation: Patients who were treated for psychiatric disorders, epilepsy, and other conditions when compared to placebo were all at increased risk of suicidality. The increased risk could not be attributed to any specific demographic subgroup of patients. In the patients with epilepsy, the relative risk of suicidality was higher, compared to those patients who were given one of the medicines in the class for psychiatric or other conditions.
If starting any anti-epileptic drug, patients should be closely monitored for notable behavior changes that could indicate the emergence or worsening of suicidal thoughts, suicidal behavior or depression. Patients, their families, and caregivers should be informed by Health Care Professionals of the potential for an increase in the risk of suicidality. If any symptoms suggestive of suicidality develop, prescribers should advise patients to immediately seek medical advice.
Neuropsychiatric Adverse Events: Patients treated with **Levetiracetam** may experience fatigue, somnolence, coordination difficulties and behavioral abnormalities.
Hematologic Abnormalities: Minor decrease in total mean RBC count, mean hemoglobin and mean hematocrit were reported in patients treated with **Levetiracetam.**
Effects on Fertility: There is no human data on the effects of **Levetiracetam** on male or female fertility.
Use in Pregnancy:
It is recommended that:
- Pre-pregnancy counselling is provided to women on (AEDs) antiepileptic drugs with regard to the risk of foetal abnormalities;
- During pregnancy AEDs should be continued and as the risk of abnormality is greater in women taking combined medication, monotherapy should be used if possible at the lowest effective dose;
- Four weeks prior to conception and for twelve weeks after conception, folic acid supplementation (5mg) should be taken;
- For the pregnant patient taking AED's, specialist prenatal diagnosis together with detailed mid-trimester ultrasound should be undertaken and offered.

Insufficient clinical data to date, on exposed pregnancies are available. Only if the potential benefit justifies the potential risk to the fetus should **Levetiracetam** be used during pregnancy. Physiological changes during pregnancy may affect **Levetiracetam** concentration, as with other antiepileptic drugs. Reports of decreased **Levetiracetam** concentrations have been reported during pregnancy.
Use in Lactation:
In human breast milk, **Levetiracetam** is excreted. A decision should be made whether to discontinue breastfeeding or discontinue **Levetiracetam** because of the potential for serious adverse reactions in breastfeeding infants. Such a decision should take into account the importance of **Levetiracetam** to the mother.
Effects on Ability to Drive or Use Machines:
No studies have been completed to evaluate the effects of **Levetiracetam** on the ability of **Levetiracetam** patients to drive and use machines.

DRUG INTERACTIONS:
Levetiracetam is unlikely to produce, or be subject to pharmacokinetic interactions.

ADVERSE EFFECTS:
Partial Onset Seizures: Adverse reactions that occurred in 1% of the patients treated with **Levetiracetam** include somnolence, asthenia, headache, dizziness, pain, depression, nervousness, ataxia, vertigo, anorexia, pharyngitis, and rhinitis.
Myoclonic Seizures: Adverse reactions that occurred in at least 5% of patients with juvenile myoclonic epilepsy include somnolence, pharyngitis, vertigo, depression, neck pain.
Primary Generalized Tonic Clonic Seizures: Adverse events that occurred in at least 5% of patients treated with **Levetiracetam** include nasopharyngitis, fatigue, diarrhea, irritability, mood swings.
Post marketing Experience: Adverse events reported for **Levetiracetam** include abnormal liver functions, agranulocytosis, pancytopenia, leukopenia, and thrombocytopenia, drug reaction with eosinophilia, dyskinesia, eythema multiforme, hepatitis, hepatic failure, pancreatitis, muscular weakness, weight loss, and alopecia.

OVERDOSAGE:
Levetiracetam has no specific antidote for overdose. The stomach may be emptied by gastric lavage or by induction of emesis after an acute overdose. Symptomatic treatment will be required for an overdose and may include haemodialysis. Standard hemodialysis procedures result in significant clearance of Levetiracetam (approximately 50% in 4 hours) and should be considered in cases of overdose.

INSTRUCTIONS FOR TABLET:
- Store below 30°C.
- Protect from heat, sunlight & moisture.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only.

INSTRUCTIONS FOR SYRUP :
- Store below 30°C.
- Protect from heat, sunlight & moisture.
- Shake well before use.
- Keep bottle tightly closed after use.
- To calculate right amount of dose, use the given dropper.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:
Epicetam Tablet 250 mg : Pack of 1 x 10 Tablets.
Epicetam Tablet 500 mg : Pack of 1 x 10 Tablets.
Epicetam Tablet 750 mg : Pack of 1 x 10 Tablets.
Epicetam Syrup 100 mg / ml : 60 ml

ہدایات برائے ٹیبلیٹ :

۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف ڈاکٹر کے نسخہ پر فروخت کریں۔

ہدایات برائے سیرپ :

۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
استعمال سے قبل بوتل کو اچھی طرح ہلا لیں۔
استعمال کے بعد بوتل کو اچھی طرح بند کر کے رکھیں۔
دوا کی صحیح مقدار جانچنے کے لئے دیئے گئے ڈراپر کا استعمال کریں۔ بچوں کی پہنچ سے دور رکھیں۔
صرف ڈاکٹر کے نسخہ پر فروخت کریں۔

FOR FURTHER INFORMATION PLEASE CONTACT:

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