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EPICETAM®

(Levetiracetam) **500 mg / 5 ml Injection**

I.V

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COMPOSITION:
Each 5 ml ampoule contains:
Levetiracetam USP ..... 500 mg.

Product Specs.: USP

DESCRIPTION:
Epicetam injection is an antiepileptic drug available as a clear, colorless, sterile solution (100 mg/mL) for intravenous administration.

CLINICAL PHARMACOLOGY:
Mechanism of action:
The precise mechanism(s) by which Levetiracetam exerts its antiepileptic effect is unknown.
Pharmacokinetics:
Equivalent doses of intravenous (I.V) Epicetam and oral Epicetam result in equivalent C_{max}, C_{min} and total systemic exposure to Epicetam when the I.V Epicetam is administered as a 15 minute infusion. Epicetam 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.
Special Populations:
Elderly:
Dose adjustment is needed in elderly patients due to decrease in renal function in elderly patients.
Pediatric patients:
Safety and effectiveness of Epicetam injection in patients below the age of 16 years have not been established.
Gender:
Epicetam C_{max} and AUC were 20% higher in women (N=11) compared to men (N=12). However, clearances adjusted for body weight were comparable.
Renal impairment:
Dosage should be reduced in patients with impaired renal function receiving Epicetam, and supplemental doses should be given to patients after dialysis.
Hepatic impairment:
No dose adjustment is needed for patients with hepatic impairment.

INDICATIONS AND USAGE:
Epicetam injection is an alternative for adult patients (16 years and older) when oral administration is temporarily not feasible.
Partial onset seizures:
Epicetam is indicated as adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy.
Myoclonic seizures in patients with juvenile myoclonic epilepsy:
Epicetam is indicated as adjunctive therapy in the treatment of myoclonic seizures in adults with juvenile myoclonic epilepsy.
Primary generalized tonic-clonic seizures:
Epicetam is indicated as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults with idiopathic generalized epilepsy.

DOSAGE AND ADMINISTRATION:
Epicetam injection is for intravenous use only and must be diluted prior to administration. Epicetam injection (500 mg/5 mL) should be diluted in 100 mL of a compatible diluent and administered intravenously as a 15 minute I.V infusion. Any unused portion of the Epicetam injection contents should be discarded.
Initial exposure to epicetam:
Epicetam can be initiated with either intravenous or oral administration.
Partial onset seizures:
Treatment should be initiated with a daily dose of 1000 mg/day, given as twice-daily dosing (500 mg twice daily). Additional dosing increments may be given (1000 mg/day additional every 2 weeks) to a maximum recommended daily dose of 3000 mg. There is no evidence that doses greater than 3000 mg/day confer additional benefit.
Myoclonic seizures in patients 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.
Primary generalized tonic-clonic seizures:
Treatment should be initiated with a dose of 1000 mg/day, given as twice-daily dosing (500 mg BID). Dosage should be increased by 1000 mg/day every 2 weeks to the recommended daily dose of 3000 mg.
Replacement therapy:
When switching from oral Epicetam, the initial total daily intravenous dosage of Epicetam should be equivalent to the total daily dosage and frequency of oral Epicetam and should be administered as a 15-minute intravenous infusion following dilution in 100mL of a compatible diluents
Switching to oral dosing:
At the end of the intravenous treatment period, the patient may be switched to Epicetam oral administration at the equivalent daily dosage and frequency of the intravenous administration.
Dosing Instructions: Epicetam injection is for intravenous use only and must be diluted prior to administration. Epicetam injection contains 500 mg Levetiracetam (500 mg/5 mL). See Table 1 for the recommended preparation and administration of Epicetam injection to achieve a dose of 500 mg, 1000 mg and 1500 mg.

Table 1: Preparation and Administration of Epicetam:

Dose	Withdraw Volume	Volume of Diluent	Infusion Time
500 mg	5 mL (injection)	100 mL	15 minutes
1000 mg	10 mL (two 5 mL injection)	100 mL	15 minutes
1500 mg	15 mL (three 5 mL injection)	100 mL	15 minutes

For example, to prepare a 1000 mg dose, dilute 10 mL of Epicetam injection in 100 mL of compatible diluents and administer intravenously as a 15-minute infusion.
Adult patients with impaired renal function:
Epicetam dosing must be individualized according to the patient's renal function status. Recommended doses and adjustment for dose for adults are shown in Table 2.

Table 2: 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

Following dialysis, a 250 to 500 mg supplemental dose is recommended.
Compatibility and stability:
EPICETAM injection was found to be physically compatible and chemically stable when mixed with the following diluents and antiepileptic drugs for at least 24 hours and stored in polyvinyl chloride (PVC) bags at controlled room temperature 15-30ºC (59-86ºF).
Diluents:
Sodium chloride (0.9%) injection, USP
Lactated Ringer's injection
Dextrose 5% injection, USP
Other antiepileptic drugs:
Lorazepam
Diazepam
Valproate sodium
There is no data to support the physical compatibility of Epicetam injection with antiepileptic drugs

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that are not listed above. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS:
Psychiatric reactions: Levetiracetam may cause behavioral abnormalities in some patients. A total of 13.3% patients treated with Levetiracetam experienced non-psychotic behavioral symptoms such as aggression, agitation, anger, anxiety, apathy, depersonalization, depression, emotional liability, hostility, irritability and nervousness. 1% of patients treated with Levetiracetam experienced psychotic symptoms. Patients should be monitored for the above signs and symptoms.

- ***somnolence & fatigue:*** 14.8% of patients treated with Levetiracetam reported somnolence while 14.7% reported asthenia. Patients should be monitored for these signs and symptoms and advised not to drive or operate machinery.
- ***serious dermatological reactions:*** Steven-Johnson syndrome and Toxic Epidermal Necrolysis have been reported in treated patients. The median time of onset is 14-17 days, but cases have been reported at least 4 months after initiation of therapy. Drug should be discontinued after first sign of rash.
- ***coordination difficulties:*** 3.4% of patients with partial onset seizures treated with Levetiracetam reported coordination difficulties such as ataxia, abnormal gait or in coordination.
- ***withdrawal seizures:***
  Antiepileptic drugs including Levetiracetam should be withdrawn gradually to minimize the potential of increased seizure frequency.
- ***hematologic abnormalities:***
  Minor decrease in total mean RBC count, mean hemoglobin and mean hematocrit were reported in patients treated with Levetiracetam.
- ***seizure control during pregnancy:*** Physiological changes during pregnancy may gradually decrease plasma levels of Levetiracetam especially during third trimester. Close monitoring of patients is therefore advised during pregnancy and in postpartum period.

Use in Specific Populations:
Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. EPICETAM 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 Epicetam, 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 of Epicetam injection in patients below the age of 16 years have not been established.
Use in patients with impaired renal function: Clearance of Levetiracetam is decreased in patients with renal impairment and is correlated with creatinine clearance. Caution should be taken in dosing patients with moderate and severe renal impairment and in patients undergoing hemodialysis. The dosage should be reduced in patients with impaired renal function receiving Epicetam and supplemental doses should be given to patients after dialysis. 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.

ADVERSE REACTIONS:
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, erythema multiforme, hepatitis, hepatic failure, pancreatitis, muscular weakness, weight loss, and alopecia.

DRUG INTERACTIONS:
No significant interactions have been reported between Levetiracetam or its major metabolite and concomitant medications via liver cytochrome P450 isoforms, epoxide hydrolase, UDP-glucuronidation enzymes, P-glycoprotein or renal tubular secretion.

DRUG ABUSE AND DEPENDENCE:
The abuse and dependence potential of Levetiracetam has not been evaluated in human

OVERDOSAGE:
Signs, symptoms and laboratory findings of acute overdosage in humans:
Symptoms of somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma can be observed with Levetiracetam overdoses.
Treatment or management of overdose:
There is no specific antidote for overdose with Levetiracetam. Hemodialysis and general supportive care of the patient including monitoring of vital signs and observation of the patient's clinical status is indicated.

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

PRESENTATION:
Epicetam Injection I.V : 1 ampoule.

ہدایات:
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۔

FOR FURTHER INFORMATION PLEASE CONTACT.

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