Esmide
(Lacosamide) BP

TABLETS
50mg
100mg
150mg
200mg

DESCRIPTION:
The chemical name of Lacosamide, the single (R)-enantiomer, is (2R)-2-Acetamido-N-benzyl-3-methoxypropanamide. Lacosamide is a functionalized amino acid. Its molecular formula is $C_{13}H_{18}N_2O_3$ and its molecular weight is 250.30g/mol.

Esmide 50mg Tablet:
Each film-coated tablet contains: Lacosamide (BP).....50mg.
Esmide 100mg Tablet:
Each film-coated tablet contains: Lacosamide (BP).....100mg.
Esmide 150mg Tablet:
Each film-coated tablet contains: Lacosamide (BP).....150mg.
Esmide 200mg Tablet:
Each film-coated tablet contains: Lacosamide (BP).....200mg.

CLINICAL PHARMACOLOGY:
Mechanism of Action:
Lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyper-excitable neuronal membranes and inhibition of repetitive neuronal firing. Lacosamide binds to collapsin response mediator protein-2 (CRMP-2), which is involved in neuronal differentiation and control of axonal outgrowth.

Pharmacokinetics:
Lacosamide is completely absorbed after oral administration with negligible first-pass effect with a high absolute bioavailability of approximately 100%. The maximum Lacosamide plasma concentrations occur approximately 1 to 4 hour post-dose after oral dosing, and elimination half-life is approximately 13 hours. Steady state plasma concentrations are achieved after 3 days of twice daily repeated administration. After intravenous administration, Cmax is reached at the end of infusion. The volume of distribution is approximately 0.6 L/kg and thus close to the volume of total body water. Lacosamide is less than 15% bound to plasma proteins. Lacosamide is primarily eliminated from the systemic circulation by renal excretion and biotransformation.

DRUG INTERACTIONS:
Anti-Epileptic Drugs (AEDs):
Effect of Lacosamide on concomitant AEDs: Lacosamide 400mg/day had no influence on the pharmacokinetics of 600 mg/day Valproic acid and 400mg/day Carbamazepine in healthy subjects. The placebo-controlled clinical studies in patients with partial-onset seizures showed that steady-state plasma concentrations of Levetiracetam, Carbamazepine, Carbamazepine epoxide, Lamotrigine, Topiramate, Oxcarbazepine Monohydroxy Derivative, (MHD), Phenytoin, Valproic acid, Phenobarbital, Gabapentin. Clonazepam and Zonisamide were not affected by concomitant intake of Lacosamide at any dose.

Digoxin:
There was no effect of Lacosamide (400mg/day) on the pharmacokinetics of Digoxin (0.5mg once daily) in a study in healthy subjects.
Metformin:
There were no clinically relevant changes in Metformin levels following co-administration of Lacosamide (400mg/day). Metformin (500mg three times a day) had no effect on the pharmacokinetics of Lacosamide (400mg/day).
Omeprazole:
Omeprazole is a CYP2C19 substrate and inhibitor. There was no effect of Lacosamide (600mg/day) on the pharmacokinetics of Omeprazole (40mg single dose) in healthy subjects. The data indicated that Lacosamide had little inhibitory or inducing effect on CYP2C19. Omeprazole at a dose of 40mg once daily had no effect on the pharmacokinetics of Lacosamide (300mg single dose).
Oral Contraceptives:
There was no influence of Lacosamide (400mg/day) on the pharmacodynamics and pharmacokinetics of an oral contraceptive containing 0.03mg Ethinylestradiol and 0.15mg Levonorgestrel in healthy subjects, except that a 20% increase in Ethinylestradiol Cmax was observed.

INDICATIONS AND USAGE:
Partial-Onset Seizures:
Tablets:
Esmide (Lacosamide) tablets are indicated as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older.

DOSAGE AND ADMINISTRATION:
Esmide(Lacosamide) Tablets may be taken with or without food.
Tablets:
The initial dose should be 50mg twice daily (100mg per day). Lacosamide can be increased at weekly intervals by 100mg/day given as two divided doses upto the recommended maintenance dose of 200 to 400mg/day, based on individual patient response and tolerability. In clinical trials, the 600mg daily dose was not more effective than the 400 mg daily dose, and was associated with a substantially higher rate of adverse reactions.

Patients with Renal Impairment:
No dose adjustment is necessary in patients with mild to moderate renal impairment. A maximum dose of 300mg/day of Lacosamide is recommended for patients with severe renal impairment [creatinine clearance (CLCR) = 30mL/min] and in patients with end-stage renal disease. Lacosamide is effectively removed from plasma by hemodialysis.

Patients with Hepatic Impairment:
The dose titration should be performed with caution in patients with hepatic impairment. A maximum dose of 300mg/day is recommended for patients with mild or moderate hepatic impairment. Lacosamide use is not recommended in patients with severe hepatic impairment.

WARNINGS AND PRECAUTIONS:
Suicidal Behavior and Ideation:
Patients treated with any AED 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.

Dizziness and Ataxia:
Patients should be advised that Lacosamide may cause dizziness and ataxia. Accordingly, they should be advised not to drive a car or to operate other complex machinery until they are familiar with the effects of Lacosamide on their ability to perform such activities.

Cardiac Rhythm and PR interval Abnormalities:
Dose-dependent prolongations in PR interval with Lacosamide have been observed in clinical studies in patients and in healthy volunteers. In clinical trials in patients with partial-onset epilepsy, asymptomatic first-degree Atrioventricular (AV) block was observed as an adverse reaction in 0.4% (4/944) of patients randomized to receive Lacosamide and 0% (0/364) of patients randomized to receive placebo. In clinical trials in patients with diabetic neuropathy, asymptomatic first-degree AV block was observed as an adverse reaction in 0.5% (5/1023) of patients receiving Lacosamide and 0% (0/291) of patients receiving placebo.

Atrial fibrillation and Atrial flutter:
Lacosamide administration may predispose to atrial arrhythmias (atrial fibrillation or flutter), especially in patients with diabetic neuropathy and/or cardiovascular disease. Patients should be made aware of the symptoms of atrial fibrillation and flutter (e.g., palpitations, rapid pulse, shortness of breath).

Syncope:
In the short-term controlled trials of Lacosamide in epilepsy patients with no significant system illnesses, there was no increase in syncope compared to placebo. In the short-term controlled trials of Lacosamide in patients with diabetic neuropathy, 1.2% of patients who were treated with Lacosamide reported an adverse reaction of syncope or loss of consciousness, compared to 0% of placebo-treated patients with diabetic neuropathy. Most of the cases of syncope were observed in patients receiving doses above 400mg/day.

ADVERSE REACTIONS:
The incidence of adverse events that occurred in 2% of adult patients with partial-onset seizures in the total Lacosamide group are:

Blood and lymphatic system disorders: neutropenia, anemia
Cardiac disorders: palpitations
Ear and labyrinth disorders: tinnitus
Gastrointestinal disorders: constipation, dyspepsia, dry mouth, oral hypoesthesia
General disorders and administration site conditions: irritability, pyrexia, feeling drunk
Injury, poisoning, and procedural complications: fall
Musculoskeletal and connective tissue disorders: Muscle spasms
Nervous system disorders: paresthesia, cognitive disorder, hypoesthesia, dysarthria, disturbance in attention, cerebellar syndrome.
Psychiatric disorders: confusional state, mood altered, depressed mood.

Adverse reactions with intravenous administration generally appeared similar to those observed with the oral formulation, although intravenous administration was associated with local adverse events such as injection site pain or discomfort (2.5%), irritation (1%) and erythema (0.5%).

USE IN SPECIFIC POPULATIONS:

Pregnancy:
Lacosamide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery:
The effects of Lacosamide on labor and delivery in pregnant women are unknown.

Nursing Mothers:
Because many drugs are excreted into human milk, a decision should be made whether to discontinue nursing or to discontinue Lacosamide, taking into account the importance of the drug to the mother.

Pediatric Use:
The safety and effectiveness of Lacosamide in pediatric patients <17 years have not been established. No Lacosamide dose adjustment based on age is considered necessary.

Patients with Renal & Hepatic impairment:
Patients with mild to moderate hepatic & renal impairment should be observed closely during dose titration. A maximum dose of 300mg/day is recommended for such patients. Lacosamide use is not recommended in patients with severe hepatic & renal impairment. Patients with co-existing hepatic and renal impairment should be monitored closely during dose titration.

INSTRUCTIONS:
Store at 15 - 30°C. Protect from heat, light and moisture.
Keep out of the reach of children. To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:
Esmide 50mg Tablet: Blister Pack of 14's.
Esmide 100mg Tablet: Blister Pack of 14's.
Esmide 150mg Tablet: Blister Pack of 14's.
Esmide 200mg Tablet: Blister Pack of 14's.

اسمائیڈ (لَیکوسامائیڈ) ٹیبلیٹس

خوراک: دوا ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات: دوا کو **15-30°** سینٹی گریڈ پر رکھیں۔
گرمی، روشنی اور نمی سے محفوظ رکھیں۔ تمام دوائیں بچوں کی پہنچ سے دُور رکھیں۔
صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

Manufactured by:
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