# Lalap®
(Lacosamide)

50mg,100mg, 150mg,
200mg Tablets B.P.
200mg/20mL Infusion B.P.
10mg/mL Oral Solution B.P.

# لالیپ
(لیکوس امائیڈ)

۵۰ ملی گرام، ۱۰۰ ملی گرام، ۱۵۰ ملی گرام،
۲۰۰ ملی گرام ٹیبلٹس بی۔پی۔
۲۰۰ ملی گرام/۲۰ ملی لیٹر انفیوژن بی۔پی۔
۱۰ ملی گرام/ملی لیٹر اورل سلوشن بی۔پی۔

## QUALITATIVE AND QUANTITATIVE COMPOSITION

**Lalap® 50mg Tablets B.P. :** Each film-coated tablet contains: Lacosamide B.P. ..... 50mg
**Lalap® 100mg Tablets B.P. :** Each film-coated tablet contains: Lacosamide B.P. ..... 100mg
**Lalap® 150mg Tablets B.P. :** Each film-coated tablet contains: Lacosamide B.P. ..... 150mg
**Lalap® 200mg Tablets B.P. :** Each film-coated tablet contains: Lacosamide B.P. .... 200mg
**Lalap® Infusion B.P. :** Each mL contains: Lacosamide B.P. .....10mg
**Lalap® Oral Solution B.P. :** Each mL contains: Lacosamide B.P. …….....10mg

**DESCRIPTION:** Lacosamide is a white to light yellow powder. It is sparingly soluble in water and slightly soluble in acetonitrile and ethanol. Its molecular formula is $C_{13}H_{18}N_2O_3$ and its molecular weight is 250.30 g/mol.

**CLINICAL PHARMACOLOGY: Mechanism of Action:** The active substance, lacosamide (R-2-acetamido-N-benzyl-3-methoxypropionamide) is a functionalized amino acid. The precise mechanism by which lacosamide exerts its antiepileptic effect in humans remains to be fully elucidated. In vitro electrophysiological studies have shown that lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyper excitable neuronal membranes. **Pharmacodynamics:** Lacosamide protected against seizures in a broad range of animal models of partial and primary generalized seizures and delayed kindling development. In non-clinical experiments lacosamide in combination with levetiracetam, carbamazepine, phenytoin, valproate, lamotrigine, topiramate or gabapentin showed synergistic or additive anticonvulsant effects. **Pharmacokinetics: Absorption:** Lacosamide is rapidly and completely absorbed after oral administration. The oral bioavailability of lacosamide tablets is approximately 100 %. Following oral administration, the plasma concentration of unchanged lacosamide increases rapidly and reaches Cmax about 0.5 to 4 hours postdose. Lacosamide tablets and syrup are bioequivalent. Food does not affect the rate and extent of absorption. **Distribution:** The volume of distribution is approximately 0.6 L/kg. Lacosamide is less than 15 % bound to plasma proteins. **Biotransformation:** 95 % of the dose is excreted in the urine as lacosamide and metabolites. The metabolism of lacosamide has not been completely characterised. The major compounds excreted in urine are unchanged lacosamide (approximately 40 % of the dose) and its Odesmethyl metabolite less than 30 %. **Elimination:** Lacosamide is primarily eliminated from the systemic circulation by renal excretion and biotransformation. After oral and intravenous administration of radiolabeled lacosamide, approximately 95 % of radioactivity administered was recovered in the urine and less than 0.5 % in the faeces. The elimination half-life of lacosamide is approximately 13 hours.

**INDICATIONS AND USAGE:** Lalap is indicated as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in adults, adolescents and children from 4 years of age with epilepsy.

**CONTRAINDICATIONS:** - Hypersensitivity to the active substance or to any of the excipients.
- Known second- or third-degree atrioventricular (AV) block.

**INTERACTIONS: Strong CYP3A4 or CYP2C9 Inhibitors:** Patients with renal or hepatic impairment who are taking strong inhibitors of CYP3A4 and CYP2C9 may have a significant increase in exposure to Lalap. Dose reduction may be necessary in these patients. **Concomitant Medications that Prolong PR Interval:** LACOSAMIDE should be used with caution in patients on concomitant medications that prolong PR interval, because of a risk of AV block or bradycardia, e.g., beta-blockers and calcium channel blockers. In such patients, obtaining an ECG before beginning LACOSAMIDE, and after LACOSAMIDE is titrated to steady-state, is recommended. In addition, these patients should be

closely monitored if they are administered Lalap through the intravenous route.

**USE IN SPECIFIC POPULATION: Pregnancy:** Lacosamide should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the fetus). If women decide to become pregnant, the use of this product should be carefully re-evaluated. **Breastfeeding:** It is unknown whether lacosamide is excreted in human breast milk. For precautionary measures, breast-feeding should be discontinued during treatment with lacosamide. **Pediatric Use:** Safety and effectiveness of Lacosamide tablets and oral solution have been established in pediatric patients 4 to less than 17 years of age. Safety of Lacosamide injection in pediatric patients has not been established. **Geriatric Use:** No LACOSAMIDE dose adjustment based on age is necessary. In elderly patients, dose titration should be performed with caution, usually starting at the lower end of the dosing range, reflecting the greater frequency of decreased hepatic function, decreased renal function, increased cardiac conduction abnormalities or polypharmacy. **Renal patient:** In all patients with renal impairment, dose titration should be performed with caution. LACOSAMIDE is effectively removed from plasma by hemodialysis. **Hepatic patients:** Lacosamide use is not recommended in patients with severe hepatic impairment.

**WARNINGS AND PRECAUTIONS**: **Suicidal behavior and Ideation:** Antiepileptic drugs (AEDs), including LACOSAMIDE, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. 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:** Treatment with lacosamide has been associated with dizziness which could increase the occurrence of accidental injury or falls. It may also cause ataxia. **Cardiac Rhythm and Conduction Abnormalities:** LACOSAMIDE should be used with caution in patients with known conduction problems (e.g., marked first-degree AV block, second-degree or higher AV block and sick sinus syndrome without pacemaker), sodium channelopathies (e.g., Brugada Syndrome), on concomitant medications that prolong PR interval, or with severe cardiac disease such as myocardial ischemia or heart failure, or structural heart disease. **Syncope:** 1.2% of patients who were treated with Lacosamide reported an adverse reaction of syncope or loss of  loss of consciousness, compared with 0% of placebo treated patients with diabetic neuropathy. **Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multi-Organ Hypersensitivity:** Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multi-organ hypersensitivity, has been reported with other antiepileptics. Some of these events have been fatal or life threatening. It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. LACOSAMIDE should be discontinued if an alternative etiology for the signs or symptoms cannot be established. **Potential for electro-clinical worsening in specific paediatric epilepsy syndromes:** The safety and efficacy of lacosamide in paediatric patients with epilepsy syndromes in which focal and generalised seizures may coexist have not been determined. **Excipients:** Excipients which may cause intolerance: Lacosamide syrup contains sodium methyl parahydroxybenzoate (E219), which may cause allergic reactions (possibly delayed). Lacosamide syrup contains sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take this medicine. Lacosamide syrup contains aspartame (E951), a source of phenylalanine, which may be harmful for people with phenylketonuria. Lacosamide syrup contains sodium. To be taken into consideration by patients on a controlled sodium diet.

**ADVERSE REACTIONS:** The following serious adverse reactions are as • Suicidal Behavior and Ideation • Dizziness and Ataxia • Cardiac Rhythm and Conduction Abnormalities • Syncope • Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity Reactions. **Very common:** Dizziness, headache, Diplopia, nausea. **Common:** Depression, confusional state, Insomnia, Balance disorder, Coordination abnormal, Memory impairment, Cognitive disorder, Somnolence, Tremor, Nystagmus, Hypoesthesia, Dysarthria, Disturbance in attention, Paraesthesia, vision blurred, Vertigo, Tinnitus, Vomiting, Constipation, Flatulence, Dyspepsia, Dry mouth, Diarrhoea, Pruritus, rash, muscle spasm, Gait disturbance, Asthenia, Fatigue, Irritability, Feeling drunk. Fall, Skin laceration, Contusion. **Uncommon:** Atrioventricular block, Bradycardia, Atrial Fibrillation, Atrial Flutter, Liver function test abnormal, Hepatic enzyme increased (> 2x ULN), Angioedema, Urticaria, Syncope. **Not unknown:** Agranulocytosis, Convulsion.

**DOSAGE AND ADMINISTRATION: Adjunctive treatment of focal seizures with or without second-**

**ary generalisation BY MOUTH OR BY INTRAVENOUS INFUSION: Child 16–17 years:** Initially 50 mg twice daily, infusion to be administered over 15–60 minutes (for up to 5 days), then increased, if tolerated, in steps of 50 mg twice daily, adjusted according to response, dose to be increased in weekly intervals; maintenance 100 mg twice daily (max. per dose 200 mg twice daily). **Adult:** Initially 50 mg twice daily, infusion to be administered over 15–60 minutes (for up to 5 days), then increased, if tolerated, in steps of 50mg twice daily, adjusted according to response, dose to be increased in weekly intervals; maintenance 100 mg twice daily (max. per dose 200 mg twice daily). Adjunctive treatment of focal seizures with or without secondary generalisation (alternative loading dose regimen when it is necessary to rapidly attain therapeutic plasma concentrations) (under close medical supervision).

**BY MOUTH OR BY INTRAVENOUS INFUSION: Child 16–17 years:** Loading dose 200mg, infusion to be administered over 15–60 minutes (for up to 5 days), followed by maintenance 100mg twice daily, to be given 12 hours after initial dose, then increased, if tolerated, in steps of 50 mg twice daily (max. per dose 200 mg twice daily), adjusted according to response, dose to be increased in weekly intervals. **Adult:** Loading dose 200mg, infusion to be administered over 15–60 minutes (for up to 5 days), followed by maintenance 100mg twice daily, to be given 12 hours after initial dose, then increased, if tolerated, in steps of 50mg twice daily (max. per dose 200mg twice daily), adjusted according to response, dose to be increased in weekly intervals. Recommended Dosage for Pediatric Patients 4 Years and older*

| Age and Body Weight | Initial Dosage | Titration Regimen | Maintenance Dosage |
|---|---|---|---|
| Pediatric patients weighing 50 kg or more | 50 mg twice daily (100 mg per day) | Increase by 50mg twice daily (100 mg per day) every week | Monotherapy: 150 mg to 200 mg twice daily (300 mg to 400 mg per day)<br>Adjunctive Therapy: 100 mg to 200 mg twice daily (200 mg to 400 mg per day) |
| Pediatric patients weighing 30 kg to less than 50 kg | 1 mg/kg twice daily (2 mg/kg/day) | Increase by 1 mg/kg twice daily (2 mg/kg/day) every week | 2 mg/kg to 4 mg/kg twice daily (4 mg/kg/day to 8 mg/kg/day) |
| Pediatric patients weighing 11 kg to less than 30kg | 1 mg/kg twice daily (2 mg/kg/day) | Increase by 1 mg/kg twice daily (2 mg/kg/day) every week | 3 mg/kg to 6 mg/kg twice daily (6 mg/kg/day to 12 mg/kg/day) |

***when not specified, the dosage is the same for monotherapy and adjunctive therapy**

**Converting from a Single Antiepileptic (AED) to Lacosamide Monotherapy:** For patients who are already on a single AED and will convert to Lacosamide monotherapy, withdrawal of the concomitant AED should not occur until the therapeutic dosage of Lacosamide is achieved and has been administered for at least 3 days. A gradual withdrawal of the concomitant AED over at least 6 weeks is recommended. **Dosage Information for Patients with Renal Impairment:** For patients with mild to moderate renal impairment, no dosage adjustment is necessary. For patients with severe renal impairment [creatinine clearance (CLCR) less than 30 mL/min as estimated by the Cockcroft-Gault equation for adults; CLCR less than 30 mL/min/1.73m2 as estimated by the Schwartz equation for pediatric patients] or end-stage renal disease, a reduction of 25% of the maximum dosage is recommended. In all patients with renal impairment, the dose titration should be performed with caution. **Hemodialysis:** Lacosamide is effectively removed from plasma by hemodialysis. Following a 4-hour hemodialysis treatment, dosage supplementation of up to 50% should be considered. **Concomitant Strong CYP3A4 or CYP2C9 Inhibitors:** Dose reduction may be necessary in patients with renal impairment who are taking strong inhibitors of CYP3A4 and CYP2C9. **Dosage Information for Patients with Hepatic Impairment:** For patients with mild or moderate hepatic impairment, a reduction of 25% of the maximum dosage is recommended. The dose titration should be performed with caution in patients with hepatic impairment. Lacosamide use is not recommended in patients with severe hepatic impairment. Concomitant Strong CYP3A4 and CYP2C9 Inhibitors Dose reduction may be necessary in patients with hepatic impairment who are taking strong inhibitors of CYP3A4 and CYP2C9 withdrawal of the concomitant AED over at least 6 weeks is recommended. **Administration Instructions for LALAP Tablets and Syrup** LALAP may be taken with or without food. **Overdosage:** Events reported after an intake of more than 800 mg (twice the maximum recommended daily dosage) of

LACOSAMIDE include dizziness, nausea, and seizures (generalized tonic-clonic seizures, status epilepticus). Cardiac conduction disorders, confusion, decreased level of consciousness, cardiogenic shock, and coma have also been observed. Fatalities have occurred following lacosamide overdoses of several grams. Reference ID: 4176722 There is no specific antidote for overdose with lacosamide. Standard decontamination procedures should be followed. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of patient. A Certified Poison Control Center should be contacted for up to date information on the management of overdose with LACOSAMIDE. Standard hemodialysis procedures result in signifi-cant clearance of LACOSAMIDE (reduction of systemic exposure by 50% in 4 hours). Hemodialysis may be indicated based on the patient's clinical state or in patients with significant renal impairment.

## DOSAGE

As directed by the physician.

## INSTRUCTIONS

For Tablets: Store below 25°C. Protect from heat, light and moisture. For Oral Solution and Infusion: Store below 25°C. Protect from heat and light. Discard any unused Solution remaining after 7 weeks of first opening the bottle. Keep all medicines out of the reach of children.

## PRESENTATION

Lalap® Tablets 50mg are available in Alu-Alu blister pack of 4x7's. Lalap® Tablets 100mg are available in Alu-Alu blister pack of 4x7' s. Lalap® Tablets 150mg are available in Alu-Alu blister pack of 2x7's. Lalap® Tablets 200mg are available in Alu-Alu blister pack of 2x7's. Lalap® Infusion 200mg/20mL is available in pack of 1x1's. Lalap® Oral Solution is available in 100mL amber pet bottle.

علامات/طریقہ استعمال:

لالیپ مرگی اور مرگی کے جزوی دوروں کے مریضوں میں مونوتھراپی اور ایڈ جنکٹ تھراپی کے طور پر تجویز کردہ ہے۔

مضر اثرات:

خودکش نظریہ، غنودگی، سردرد، دھندلاپن، متلی، ڈپریشن، نیند نہ آنا، چکر، پرورائٹس، توازن کی خرابی، دست، اُلٹی، تھکان۔

احتیاطی تدابیر:

حاملہ خواتین میں لیکوس امائیڈ کا استعمال ممنوع ہے۔ انتہائی ضرورت پڑنے پر صرف ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

دودھ پلانے والی ماؤں میں لیکوس امائیڈ کا استعمال ممنوع ہے۔

فینائل کیٹون یوریا کے مریضوں میں لیکوس امائیڈ کا استعمال نقصان دہ ہوسکتا ہے۔

فرکٹوس انٹولیرنس کے مریضوں میں لیکوس امائیڈ کا استعمال الرجی کا باعث بن سکتا ہے۔

سوڈیم کنٹرولڈ ڈائیٹ کے مریض احتیاط سے استعمال کریں۔

ابتدائی طور پر خوراک کا استعمال کم مقدار میں شروع کروائیں اور بتدریج مقدار کو گھٹا کے استعمال کو روک دیں۔

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات: لالیپ ٹیبلٹس: ۲۵ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔ روشنی، گرمی اور نمی سے محفوظ رکھیں۔

لالیپ انفیوژن، لالیپ اورل سلوشن: ۲۵ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

روشنی اور گرمی سے محفوظ رکھیں۔

بوتل کھلنے کے ۷ ہفتوں کے اندر استعمال کرلیں۔ غیر استعمال شدہ سلوشن ضائع کردیں۔

تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔

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ISO 9001:2015 ISO 14001:2015 ISO 45001:2018

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