

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LACOSAMIDE TABLETS safely and effectively. See full prescribing information for LACOSAMIDE TABLETS and LACOSAMIDE TABLETS.

LACOSAMIDE tablets, for oral use, (V)
Initial U.S. Approval: 2008

RECENT MAJOR CHANGES

Indications and Usage (1)	08/2014
Dosage and Administration (2)	08/2014
Warnings and Precautions (5.3, 5.4)	08/2014

INDICATIONS AND USAGE

Lacosamide is indicated as adjunctive therapy in patients with partial-onset seizures (1)

DOSAGE AND ADMINISTRATION

- Adjunctive Therapy:** Initial recommended dose is 50 mg twice daily, based on individual patient response and tolerability, increase at weekly intervals by 50 mg twice daily, up to a recommended maintenance dose of 100 mg to 200 mg twice daily (2.1)
- Renal Impairment:** Dose adjustment is recommended for patients with severe renal impairment (creatinine clearance < 30 mL/min) (2.3, 12.3)
- Hepatic Impairment:** Dose adjustment is recommended for patients with mild or moderate hepatic impairment; use in severe hepatic impairment patients is not recommended (2.4, 12.3)

DOSAGE FORMS AND STRENGTHS

- 50 mg (light pink), 100 mg (yellow), 150 mg (orange), 200 mg (blue) film-coated tablets (3)



Lacosamide Tablets
50 mg, 100 mg,
150 mg and 200 mg

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Monitor patients for suicidal behavior and ideation (5.1)
- Lacosamide may cause dizziness and ataxia (5.2)
- Cardiac Rhythm and Conduction Abnormalities: ECG before beginning lacosamide, and after lacosamide is titrated to steady-state maintenance dose is recommended in patients with known cardiac conduction problems, taking drugs known to induce PR interval prolongation, or with severe cardiac disease (5.3)
- Lacosamide may cause syncope (5.4)
- Lacosamide should be gradually withdrawn to minimize the potential of increased seizure frequency (5.5)
- Multifactorial Hypersensitivity Reactions (5.6)

ADVERSE REACTIONS

- Adjunctive therapy:** Most common adverse reactions (> 10% and greater than placebo) are diplopia, headache, dizziness, nausea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-818-4555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

USE IN SPECIFIC POPULATIONS

- Pregnancy:** Based on animal data, may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 04/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Lacosamide tablets are indicated in patients 17 years and older with partial-onset seizures as adjunctive therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Lacosamide Tablet

Adjunctive Therapy

The initial recommended dose is 50 mg twice daily (100 mg per day), based on individual patient response and tolerability. The dose can be increased at weekly intervals by 50 mg twice daily (100 mg per day). The recommended maintenance dose is 100 mg twice daily to 200 mg twice daily (200 mg to 400 mg per day). In clinical trials, the 300 mg twice daily (600 mg per day) dose was not more effective than the 200 mg twice daily dose (400 mg per day), but was associated with a substantially higher rate of adverse reactions.

When discontinuing lacosamide tablets, a gradual withdrawal over at least 1 week is recommended (see Warnings and Precautions (5.3)).

2.3 Dosage Information in Patients with Renal Impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment. A maximum dose of 300 mg per day lacosamide is recommended for patients with severe renal impairment (creatinine clearance (CL_{cr}) less than or equal to 30 mL/min) and in patients with endstage renal disease. Lacosamide is effectively removed from plasma by hemodialysis. Following a 4-hour hemodialysis treatment, dosage supplementation of up to 50% should be considered. In already impaired patients, the dose titration should be performed with caution. Patients with renal impairment who are taking strong inhibitors of CYP3A4 and CYP2C9 may have a significant increase in exposure to lacosamide. Dose reduction may be necessary in these patients (see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)).

2.4 Dosage Information in Patients with Hepatic Impairment

The dose titration should be performed with caution in patients with hepatic impairment. A maximum dose of 300 mg per day is recommended for patients with mild or moderate hepatic impairment.

Lacosamide tablets use is not recommended in patients with severe hepatic impairment. Patients with hepatic impairment who are taking strong inhibitors of CYP3A4 and CYP2C9 may have a significant increase in exposure to lacosamide. Dose reduction may be necessary in these patients (see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)).

2.5 Administration Instructions

Lacosamide tablets may be taken with or without food.

3 DOSAGE FORMS AND STRENGTHS

50mg (light pink), 100 mg (yellow), 150mg (orange), and 200 mg (blue) film-coated tablets

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 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.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI: 1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number of events is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed.

Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1 Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events Per 1,000 Patients	Drug Patients with Events Per 1,000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1,000 Patients
Epilepsy	3.4	3.5	2.4	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

Folding for Bottle pack
Open size : 350x500 mm
Close size : 37x37 mm

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the premarketing development of adjunctive therapy for partial-onset seizures, 1,327 patients received lacosamide in controlled and uncontrolled trials, of whom 1,000 were treated for longer than 6 months, and 852 for longer than 12 months.

Lacosamide

Adjunctive Therapy Controlled Trials (Studies 2, 3, and 4)

In adjunctive therapy controlled clinical trials, the rate of discontinuation as a result of an adverse reaction was 5% and 17% in patients randomized to receive lacosamide at the recommended doses of 200 and 400 mg/day, respectively, 25% at 600 mg/day, and 5% in patients randomized to receive placebo. The adverse reactions most commonly (>1% on lacosamide and greater than placebo) leading to discontinuation were dizziness, ataxia, vomiting, diplopia, nausea, vertigo, and blurred vision.

Table 2 gives the incidence of adverse reactions that occurred in > 2% of adult patients with partial-onset seizures in the lacosamide total group and for which the incidence was greater than placebo.

Table 2: Adverse Reactions Incidence in Adjunctive Therapy Pooled, Placebo-Controlled Trials in Patients with Partial-Onset Seizures (Studies 2, 3, and 4)

System Organ Class/ Preferred Term	Placebo N=364	Lacosamide 200 mg/day N=270	Lacosamide 400 mg/day N=471	Lacosamide 600 mg/day N=203	Lacosamide Total N=944
Ear and labyrinth disorder					
Vertigo	1	5	3	4	4
Eye disorders					
Diplopia	2	6	10	16	11
Blurred Vision	3	2	9	16	8
Gastrointestinal disorders					
Nausea	4	7	11	17	11
Vomiting	3	6	9	16	9
Diarrhea	3	3	5	4	4
General disorders and administration site conditions					
Fatigue	6	7	7	15	9
Gait disturbance	<1	<1	2	4	2
Asthenia	1	2	2	4	2
Injury, poisoning and procedural complications					
Cotusion	3	3	4	2	3
Skin laceration	2	2	3	3	3
Nervous system disorders					
Dizziness	8	16	30	53	31
Headache	9	11	14	12	13
Ataxia	2	4	7	15	8
Somnolence	5	5	8	8	7
Tremor	4	4	6	12	7
Nystagmus	4	2	5	10	5
Balance disorder	0	1	5	6	4
Memory impairment	2	1	2	6	2
Psychiatric disorders					
Depression	1	2	2	2	2
Skin and subcutaneous disorders					
Pruritus	1	3	2	3	2

The overall adverse reaction rate was similar in male and female patients. Although there were few non-Caucasian patients, no differences in the incidences of adverse events compared to Caucasian patients were observed.

Laboratory Abnormalities

Abnormalities in liver function tests have occurred in controlled trials with lacosamide in adult patients with partial-onset seizures who were taking 1 to 3 concomitant anti-epileptic drugs. Elevations of ALT to >3 x ULN occurred in 0.7% (7/955) of lacosamide patients and 0% (0/255) of placebo patients. One case of hepatitis with transaminase >20 x ULN occurred in one healthy subject 10 days after lacosamide treatment completion, along with nephritis (proteinuria and urine casts). Serologic studies were negative for viral hepatitis. Transaminases returned to normal within one month without specific treatment. At the time of this event, bilirubin was normal. The hepatitis/nephritis was interpreted as a delayed hypersensitivity reaction to lacosamide.

Other Adverse Reactions

The following is a list of adverse reactions reported by patients treated with lacosamide in all clinical trials in patients with partial-onset seizures, including controlled trials and long-term open-label extension trials. Adverse reactions addressed in other tables or sections are not listed here.

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

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of lacosamide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: Agranulocytosis

Psychiatric disorders: Aggression, agitation, hallucination, insomnia, psychotic disorder

Skin and subcutaneous tissue disorders: Angioedema, rash, urticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis

7 DRUG INTERACTIONS

7.1 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 lacosamide. Dose reduction may be necessary in these patients.

7.2 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Lacosamide produced developmental toxicity (increased embryofetal and perinatal mortality, growth deficit) in rats following administration during pregnancy. Developmental neurotoxicity was observed in rats following administration during a period of postnatal development corresponding to the third trimester of human pregnancy. These effects were observed at doses associated with clinically relevant plasma exposures.

Lacosamide has been shown *in vitro* to interfere with the activity of collapsin response mediator protein-2 (CRMP-2), a protein involved in neuronal differentiation and control of axonal outgrowth. Potential related adverse effects on CNS development cannot be ruled out.

There are no adequate and well-controlled studies in pregnant women. Lacosamide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Oral administration of lacosamide to pregnant rats (20, 75, or 200 mg/kg/day) and rabbits (6.25, 12.5, or 25 mg/kg/day) during the period of organogenesis did not produce any teratogenic effects. However, the maximum doses evaluated were limited by maternal toxicity in both species and embryofetal death in rats. These doses were associated with maternal plasma lacosamide exposures [area under the plasma-time concentration curve, (AUC)] = 2 and 11 times (rat and rabbit, respectively) that in humans at the maximum recommended human dose (MRHD) of 400 mg/day.

When lacosamide (25, 70, or 200 mg/kg/day) was orally administered to rats throughout gestation, parturition, and lactation, increased perinatal mortality and decreased body weights were observed in the offspring at the highest dose. The no-effect dose for pre- and post-natal developmental toxicity in rats (70 mg/kg/day) was associated with a maternal plasma lacosamide AUC approximately equal to that in humans at the MRHD.

Oral administration of lacosamide (30, 90, or 180 mg/kg/day) to rats during the neonatal and juvenile periods of postnatal development resulted in decreased brain weights and long-term neurobehavioral changes (altered open field performance, deficits in learning and memory). The early postnatal period in rats is generally thought to correspond to late pregnancy in humans in terms of brain development. The no-effect dose for developmental neurotoxicity in rats was associated with a plasma lacosamide AUC approximately 0.5 times that in humans at the MRHD.

Pregnancy Registry

Physicians are advised to recommend that pregnant patients taking lacosamide tablets enroll in the North American Antiepileptic Drug (NAED) pregnancy registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website <http://www.aedpregnancyregistry.org/>.

8.2 Labor and Delivery

The effects of lacosamide on labor and delivery in pregnant women are unknown. In a pre- and post-natal study in rats, there was a tendency for prolonged gestation in all lacosamide treated groups at plasma exposures (AUC) at or below the plasma AUC in humans at the maximum recommended human dose of 400 mg/day.

8.3 Nursing Mothers

Studies in lactating rats have shown that lacosamide and/or its metabolites are excreted in milk. It is not known whether lacosamide is excreted in human milk. 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.

8.4 Pediatric Use

The safety and effectiveness of lacosamide in pediatric patients less than 17 years of age have not been established.

Lacosamide has been shown *in vitro* to interfere with the activity of collapsin response mediator protein-2 (CRMP-2), a protein involved in neuronal differentiation and control of axonal outgrowth. Potential related adverse effects on CNS development cannot be ruled out. Administration of lacosamide to rats during the neonatal and juvenile periods of postnatal development resulted in decreased brain weights and long-term neurobehavioral changes (altered open field performance, deficits in learning and memory). The no-effect dose for developmental neurotoxicity in rats was associated with a plasma lacosamide exposure (AUC) approximately 0.5 times the human plasma AUC at the maximum recommended human dose of 400 mg/day.

8.5 Geriatric Use

There were insufficient numbers of elderly patients enrolled in partial-onset seizure trials (n=18) to adequately assess the effectiveness of lacosamide in this population.

No lacosamide dose adjustment based on age is necessary. In elderly patients, dose titration should be performed with caution (see Clinical Pharmacology (12.3)).

8.6 Renal Impairment

A maximum dose of 300 mg per day is recommended for patients with severe renal impairment (CL_{cr} < 30 mL/min) and in patients with endstage renal disease. Lacosamide is effectively removed from plasma by hemodialysis. Dosage supplementation of up to 50% following hemodialysis should be considered. In all renally impaired patients, dose titration should be performed with caution. (see Dosage and Administration (2.3), Clinical Pharmacology (12.3)).

8.7 Hepatic Impairment

Patients with mild to moderate hepatic impairment should be observed closely during dose titration. A maximum dose of 300 mg per day is recommended for patients with mild to moderate hepatic impairment. The pharmacokinetics of lacosamide has not been evaluated in severe hepatic impairment. Lacosamide use is not recommended in patients with severe hepatic impairment. (see Dosage and Administration (2.4), Clinical Pharmacology (12.3)) Patients with co-existing hepatic and renal impairment should be monitored closely during dose titration.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Lacosamide is a Schedule V controlled substance.

9.2 Abuse

In a human abuse potential study, single doses of 200 mg and 800 mg lacosamide produced euphoric-type subjective responses that differentiated statistically from placebo; at 800 mg, these euphoric-type responses were statistically indistinguishable from those produced by alprazolam, a Schedule IV drug. The duration of the euphoric-type responses following lacosamide was less than that following alprazolam. A high rate of euphoria was also reported as an adverse event in the human abuse potential study following single doses of 800 mg lacosamide (15% (5/41)) compared to placebo (0%) and in two pharmacokinetic studies following single and multiple doses of 300 mg to 800 mg lacosamide (ranging

After oral and intravenous administration of 100 mg [14C]-lacosamide approximately 95% of radioactivity was recovered in the urine and less than 0.5% in the feces. The major compounds excreted were unchanged lacosamide (approximately 40% of the dose), its O-desmethyl metabolite (approximately 30%), and a structurally unknown polar fraction (~20%). The plasma exposure of the major human metabolite, O-desmethyl-lacosamide, is approximately 10% of that of lacosamide. This metabolite has no known pharmacological activity.

The CYP isoforms mainly responsible for the formation of the major metabolite (O-desmethyl) are CYP3A4, CYP2C8, and CYP2C19. The elimination half-life of the unchanged drug is approximately 13 hours and is not altered by different doses, multiple dosing or intravenous administration.

There is no enantiomeric interconversion of lacosamide.

Special Populations

Renal Impairment

Lacosamide and its major metabolite are eliminated from the systemic circulation primarily by renal excretion.

The AUC of lacosamide was increased approximately 25% in mild (CL_{cr} 50 to 80 mL/min) and moderately (CL_{cr} 30 to 50 mL/min) and 60% in severely (CL_{cr} < 30 mL/min) renally impaired patients compared to subjects with normal renal function (CL_{cr} > 80 mL/min), whereas C_{max} was unaffected. Lacosamide is effectively removed from plasma by hemodialysis. Following a 4-hour hemodialysis treatment, AUC of lacosamide is reduced by approximately 50% [see Dosage and Administration (2.3)].

Hepatic Impairment

Lacosamide undergoes metabolism. Subjects with moderate hepatic impairment (Child-Pugh B) showed higher plasma concentrations of lacosamide (approximately 50 to 60% higher AUC compared to healthy subjects). The pharmacokinetics of lacosamide have not been evaluated in severe hepatic impairment [see Dosage and Administration (2.4)].

Geriatric

In the elderly (>65 years), dose and body-weight normalized AUC and C_{max} is about 20% increased compared to young subjects (18 to 64 years). This may be related to body weight and decreased renal function in elderly subjects.

Gender

Lacosamide clinical trials indicate that gender does not have a clinically relevant influence on the pharmacokinetics of lacosamide.

Race

There are no clinically relevant differences in the pharmacokinetics of lacosamide between Asian, Black, and Caucasian subjects.

CYP2C19 Polymorphism

There are no clinically relevant differences in the pharmacokinetics of lacosamide between CYP2C19 poor metabolizers and extensive metabolizers. Results from a trial in poor metabolizers (PM) (N=4) and extensive metabolizers (EM) (N=9) of cytochrome P450 CYP2C19 showed that lacosamide plasma concentrations were similar in PMs and EMs, but plasma concentrations and the amount excreted into urine of the O-desmethyl metabolite were about 70% reduced in PMs compared to EMs.

Drug Interactions

In Vitro Assessment of Drug Interactions

In vitro metabolism studies indicate that lacosamide does not induce the enzyme activity of drug metabolizing cytochrome P450 isoforms CYP1A2, 2B6, 2C8, 2C9, 2C19 and 3A4. Lacosamide did not inhibit CYP 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1, 3A4/5 at plasma concentrations observed in clinical studies.

In vitro data suggest that lacosamide has the potential to inhibit CYP2C19 at therapeutic concentrations. However, an *in vivo* study with omeprazole did not show an inhibitory effect on omeprazole pharmacokinetics.

Lacosamide is not a substrate or inhibitor for P-glycoprotein.

Lacosamide is a substrate of CYP3A4, CYP2C8, and CYP2C19. Patients with renal or hepatic impairment who are taking strong inhibitors of CYP3A4 and CYP2C8 may have increased exposure to lacosamide.

Since <15% of lacosamide is bound to plasma proteins, a clinically relevant interaction with other drugs through competition for protein-binding sites is unlikely.

In Vivo Assessment of Drug Interactions

Drug Interaction studies with AEDs

- **Effect of lacosamide on concomitant AEDs:** Lacosamide 400 mg/day had no influence on the pharmacokinetics of 600 mg/day valproic acid and 400 mg/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 monohydrate derivative (MHD), phenytoin, valproic acid, phenobarbital, gabapentin, zonisamide, and zonisamide were not affected by concomitant intake of lacosamide at any dose.

- **Effect of concomitant AEDs on lacosamide:** Drug-drug interaction studies in healthy subjects showed that 600 mg/day valproic acid had no influence on the pharmacokinetics of 400 mg/day lacosamide. Likewise, 400 mg/day carbamazepine had no influence on the pharmacokinetics of lacosamide in a healthy subject study. Population pharmacokinetics results in patients with partial-onset seizures showed small reductions (15% to 20% lower) in lacosamide plasma concentrations when lacosamide was coadministered with carbamazepine, phenobarbital or phenytoin.

Drug-drug interaction studies with other drugs

Digoxin

There was no effect of lacosamide (400 mg/day) on the pharmacokinetics of digoxin (0.5 mg once daily) in a study in healthy subjects.

Metformin

There were no clinically relevant changes in metformin levels following coadministration of lacosamide (400 mg/day).

Metformin (500 mg three times a day) had no effect on the pharmacokinetics of lacosamide (400 mg/day).

Omeprazole

Omeprazole is a CYP2C19 substrate and inhibitor.

There was no effect of lacosamide (600 mg/day) on the pharmacokinetics of omeprazole (40 mg single dose) in healthy subjects. The data indicated that lacosamide had little *in vivo* inhibitory or inducing effect on CYP2C19.

Omeprazole at a dose of 40 mg once daily had no effect on the pharmacokinetics of lacosamide (300 mg single dose). However, plasma levels of the O-desmethyl metabolite were reduced about 50% in the presence of omeprazole.

Midazolam

Midazolam is a 3A4 substrate.

There was no effect of lacosamide (200 mg single dose or repeat doses of 400 mg/day given as 200 mg BID) on the pharmacokinetics of midazolam (single dose, 7.5 mg), indicating no inhibitory or inducing effects on CYP3A4.

Oral Contraceptives

There was no influence of lacosamide (400 mg/day) on the pharmacodynamics and pharmacokinetics of an oral contraceptive containing 0.05 mg ethinylestradiol and 0.15 mg levonorgestrel in healthy subjects, except that a 20% increase in ethinylestradiol C_{max} was observed.

Warfarin

Coadministration of lacosamide (400 mg/day) with warfarin (25 mg single dose) did not result in a clinically relevant change in the pharmacokinetic and pharmacodynamic effects of warfarin in a study in healthy male subjects.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of drug related carcinogenicity in mice or rats. Mice and rats received lacosamide once daily by oral administration for 104 weeks at doses producing plasma exposures (AUC) up to approximately 1 and 3 times, respectively, the plasma AUC in humans at the maximum recommended human dose (MRHD) of 400 mg/day.

Lacosamide was negative in an *in vitro* Ames test and an *in vivo* mouse micronucleus assay. Lacosamide induced a positive response in the *in vitro* mouse lymphoma assay.

No adverse effects on male or female fertility or reproduction were observed in rats at doses producing plasma exposures (AUC) up to approximately 2 times the plasma AUC in humans at the MRHD.

14 CLINICAL STUDIES

14.2 Adjunctive Therapy in Patients with Partial-Onset Seizures

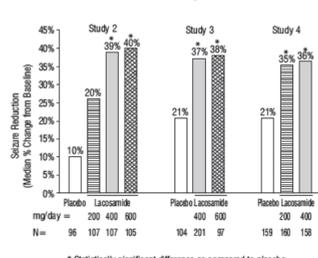
The efficacy of lacosamide as adjunctive therapy in partial-onset seizures was established in three 12-week, randomized, double-blind, placebo-controlled, multicenter trials in adult patients (Study 2, Study 3, and Study 4). Enrolled patients had partial-onset seizures with or without secondary generalization, and were not adequately controlled with 1 to 3 concomitant AEDs. During an 8-week baseline period, patients were required to have an average of ≥ 4 partial-onset seizures per 28 days with no seizure-free period exceeding 21 days. In these 3 trials, patients had a mean duration of epilepsy of 24 years and a median baseline seizure frequency ranging from 10 to 17 per 28 days. 84% of patients were taking 2 to 3 concomitant AEDs with or without concurrent vagal nerve stimulation.

Study 2 compared doses of lacosamide 200, 400, and 600 mg/day with placebo. Study 3 compared doses of lacosamide 400 and 600 mg/day with placebo. Study 4 compared doses of lacosamide 200 and 400 mg/day with placebo. In all three trials, following an 8-week baseline phase to establish baseline seizure frequency prior to randomization, patients were randomized and titrated to the randomized dose (a 1-step back-titration of lacosamide 100 mg/day or placebo was allowed in the case of intolerable adverse events at the end of the titration phase). During the titration phase, in all 3 adjunctive therapy trials, treatment was initiated at 100 mg/day (50 mg twice daily), and increased in weekly increments of 100 mg/day to the target dose. The titration phase lasted 6 weeks in Study 2 and Study 3, and 4 weeks in Study 4. In all three trials, the titration phase was followed by a maintenance phase that lasted 12 weeks, during which patients were to remain on a stable dose of lacosamide.

A reduction in 28 day seizure frequency (baseline to maintenance phase), as compared to the placebo group, was the primary variable in all three adjunctive therapy trials. A statistically significant effect was observed with lacosamide treatment (Figure 1) at doses of 200 mg/day (Study 4), 400 mg/day (Studies 2, 3, and 4), and 600 mg/day (Studies 2 and 3).

Subst evaluations of lacosamide demonstrate no important differences in seizure control as a function of gender or race, although data on race was limited (about 10% of patients were non-Caucasian).

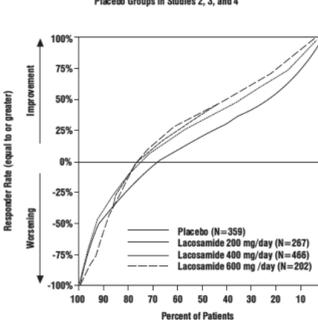
Figure 1 – Median Percent Reduction in Seizure Frequency per 28 days from Baseline to the Maintenance Phase by Dose



* Statistically significant difference as compared to placebo.

Figure 2 presents the percentage of patients (X-axis) with a percent reduction in partial seizure frequency (responder rate) from baseline to the maintenance phase at least as great as that represented on the Y-axis. A positive value on the Y-axis indicates an improvement from baseline (i.e., a decrease in seizure frequency), while a negative value indicates a worsening from baseline (i.e., an increase in seizure frequency). Thus, in a display of this type, a curve for an effective treatment is shifted to the left of the curve for placebo. The proportion of patients achieving any particular level of reduction in seizure frequency was consistently higher for the lacosamide groups, compared to the placebo group. For example, 40% of patients randomized to lacosamide (400 mg/day) experienced a 50% or greater reduction in seizure frequency, compared to 23% of patients randomized to placebo. Patients with an increase in seizure frequency > 100% are represented on the Y-axis as equal to or greater than -100%.

Figure 2 – Proportion of Patients by Responder Rate for Lacosamide and Placebo Groups in Studies 2, 3, and 4



16 HOW SUPPLIED/STORAGE AND HANDLING

Lacosamide tablets 50 mg are light pink color, oval, bicovex, film-coated tablets debossed with "919" on one side and plain on other side. They are supplied as follows:

Bottles of 60 with Child-Resistant Cap.....NDC 47335-919-86
Bottles of 180 with Child-Resistant Cap.....NDC 47335-919-82
Bottles of 1000 with Non Child-Resistant Cap.....NDC 47335-919-18

Lacosamide tablets 100 mg are yellow, oval, bicovex, film-coated tablets debossed with "922" on one side and plain on other side. They are supplied as follows:

Bottles of 60 with Child-Resistant Cap.....NDC 47335-922-86
Bottles of 180 with Child-Resistant Cap.....NDC 47335-922-82
Bottles of 1000 with Non Child-Resistant Cap.....NDC 47335-922-18

Lacosamide tablets 150 mg are orange, oval, bicovex, film-coated tablets debossed with "943" on one side and plain on other side. They are supplied as follows:

Bottles of 60 with Child-Resistant Cap.....NDC 47335-943-86
Bottles of 180 with Child-Resistant Cap.....NDC 47335-943-82
Bottles of 1000 with Non Child-Resistant Cap.....NDC 47335-943-18

Lacosamide tablets 200 mg are blue, oval, bicovex, film-coated tablets debossed with "980" on one side and plain on other side. They are supplied as follows:

Bottles of 60 with Child-Resistant Cap.....NDC 47335-980-86
Bottles of 180 with Child-Resistant Cap.....NDC 47335-980-82
Bottles of 1000 with Non Child-Resistant Cap.....NDC 47335-980-18

16.1 Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Suicidal Thinking and Behavior

Patients, their caregivers, and families should be counseled that AEDs, including lacosamide tablets, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Dizziness and Ataxia

Patients should be counseled that lacosamide tablets use may cause dizziness, double vision, abnormal coordination and balance, and somnolence. Patients taking lacosamide tablets should be advised not to drive, operate complex machinery, or engage in other hazardous activities until they have become accustomed to any such effects associated with lacosamide tablets.

Cardiac Rhythm and Conduction Abnormalities
Patients should be aware that lacosamide tablets are associated with electrocardiographic changes that may predispose to irregular beat and syncope, particularly in patients with underlying cardiovascular disease, with heart conduction problems or who are taking other medications that affect the heart. Patients who develop syncope should lay down with raised legs and contact their health care provider.

Multisystem Hypersensitivity Reactions
Patients should be aware that lacosamide tablets may cause serious hypersensitivity reactions affecting multiple organs such as the liver and kidney. Lacosamide tablets should be discontinued if a serious hypersensitivity reaction is suspected. Patients should also be instructed to report promptly to their physicians any symptoms of liver toxicity (e.g., fatigue, jaundice, dark urine).

Pregnancy Registry
Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during lacosamide tablets therapy. Encourage patients to enroll in the North American Antiepileptic Drug (NAED) pregnancy registry if they become pregnant. This registry is collecting information about the safety of AEDs during pregnancy. To enroll, patients can call the toll free number 1-888-233-2334 [see Use in Specific Populations (8.1)].

MEDICATION GUIDE

Lacosamide (la KOE sa mide) Tablets

Read this Medication Guide before you start taking lacosamide tablets and each time you get a refill. There may be new information. This Medication Guide describes important safety information about lacosamide tablets. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about lacosamide tablets?

Do not stop taking lacosamide tablets without first talking to your healthcare provider. Stopping lacosamide tablets suddenly can cause serious problems.

Lacosamide tablets can cause serious side effects, including:

1. **Like other antiepileptic drugs, lacosamide tablets may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.**

Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting in dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
 - Keep all follow-up visits with your healthcare provider as scheduled.
 - Call your healthcare provider between visits as needed, especially if you are worried about symptoms.
 - Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.
 - **Do not stop lacosamide tablets without first talking to a healthcare provider.** Stopping lacosamide tablets suddenly can cause serious problems. Stopping secure medicine suddenly in a patient who has epilepsy can cause seizures that will not stop (status epilepticus).
2. Lacosamide tablets may cause you to feel dizzy, have double vision, feel sleepy, or have problems with coordination and walking. Do not drive, operate heavy machinery, or do other dangerous activities until you know how lacosamide tablets affect you.
3. Lacosamide tablets may cause you to have an irregular heartbeat or may cause you to faint. Call your healthcare provider if you have:
- fast, slow, or pounding heartbeat
 - shortness of breath
 - feel lightheaded
 - faintness or if you feel like you are going to faint
- If you have fainted or feel like you are going to faint you should lay down with your legs raised.

4. Lacosamide is a federally controlled substance (C-V) because it can be abused or lead to drug dependence. Keep your lacosamide tablets in a safe place, to protect it from theft. Never give your lacosamide tablets to anyone else, because it may harm them. Selling or giving away this medicine is against the law.

What are lacosamide tablets?

Lacosamide tablets are a prescription medicine that can be used with other medicines to treat partial-onset seizures in people 17 years of age and older.

It is not known if lacosamide tablets are safe and effective in children under 17 years of age.

What should I tell my healthcare provider before taking lacosamide tablets?

Before you take lacosamide tablets, tell your healthcare provider, if you:

- have or have had depression, mood problems or suicidal thoughts or behavior
- have heart problems
- have kidney problems
- have liver problems
- have shared prescription medicines, street drugs or alcohol in the past
- have any other medical problems
- are pregnant or plan to become pregnant. It is not known if lacosamide tablets can harm your unborn baby. Tell your healthcare provider right away if you become pregnant while taking lacosamide tablets. You and your healthcare provider will decide if you should take lacosamide tablets while you are pregnant.
- If you become pregnant while taking lacosamide tablets, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic medicine during pregnancy.
- are breastfeeding or plan to breastfeed. It is not known if lacosamide passes into your breast milk or if it can harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take lacosamide tablets.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Taking lacosamide tablets with certain other medicines may cause side effects or affect how well they work. Do not start or stop other medicines without talking to your healthcare provider. Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist each time you get a new medicine.

How should I take lacosamide tablets?

- Take lacosamide tablets exactly as your healthcare provider tells you.
- Your healthcare provider will tell you how many lacosamide tablets to take and when to take it.
- Your healthcare provider may change your dose if needed.
- Do not stop lacosamide tablets without first talking to a healthcare provider. Stopping lacosamide tablets suddenly in a patient who has epilepsy can cause seizures that will not stop (status epilepticus).
- Lacosamide tablets may be taken with or without food.
- If you take too many lacosamide tablets, call your healthcare provider or local Poison Control Center right away.

What should I avoid while taking lacosamide tablets?

Do not drive, operate heavy machinery, or do other dangerous activities until you know how lacosamide tablets affect you. Lacosamide tablets may cause you to feel dizzy, have double vision, feel sleepy, or have problems with coordination and walking.

What are the possible side effects of lacosamide tablets?

See "What is the most important information I should know about lacosamide tablets?"

Lacosamide tablets may cause other serious side effects including:

- Lacosamide tablets may cause a serious allergic reaction that may affect your skin or other parts of your body such as your liver or blood cells. Call your healthcare provider right away if you have:
 - a skin rash, hives
 - fever or swollen glands that do not go away
 - shortness of breath, swelling of the legs, yellowing of the skin or whites of the eyes, or dark urine.

The most common side effects of lacosamide tablets include:

- double vision
- headache
- dizziness
- nausea

These are not all of the possible side effects of lacosamide tablets. For more information ask your healthcare provider or pharmacist. Tell your healthcare provider about any side effect that bothers you or that does not go away. Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store lacosamide tablets?

- Store lacosamide tablets at 20°C to 25°C (68°F to 77°F); excursions permitted between 15° and 30°C (59° and 86°F)

Keep lacosamide tablets and all medicines out of the reach of children

General information about the safe and effective use of lacosamide tablets
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use lacosamide tablets for a condition for which it was not prescribed. Do not give lacosamide tablets to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about lacosamide tablets. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about lacosamide tablets that is written for health professionals.

For more information, call 1-800-818-4555.

What are the ingredients in lacosamide tablets?
Active ingredient: lacosamide
Inactive ingredients: Microcrystalline cellulose, low substituted hydroxypropyl cellulose, croscarmellose, hydroxypropyl cellulose, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, talc, titanium dioxide, polyethylene glycol, soya lecithin and additional ingredients listed below.

- **50 mg tablets:** red iron oxide, FD&C Blue # 2 and black iron oxide
 - **100 mg tablets:** yellow iron oxide
 - **150 mg tablets:** yellow iron oxide, red iron oxide and black iron oxide
 - **200 mg tablets:** FD&C Blue # 2
- This Medication Guide has been approved by the U.S. Food and Drug Administration.

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Manufactured by:
Sun Pharmaceutical Industries Ltd.
Survey No. 259/15,
P.O. Box, Dabra-358 191, (U.T. of D & NH), India.



Folding for Bottle pack
Open size : 350x500 mm
Close size : 37x37 mm

350 mm

Size: 350x500 mm