

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 seizure 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 affects 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
 - fainted 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 tablets are 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 is 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 abused 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 them.
- 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 between 68°F to 77°F (20°C to 25°C).

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, go to www.bpxr.com or call 1-800-367-3395.

What are the ingredients in lacosamide tablets?

Active ingredient: lacosamide

Tablet inactive ingredients: colloidal silicon dioxide, crospovidone, hydroxypropyl cellulose, lecithin, low-substituted hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide and additional ingredients listed below. Lacosamide Tablets are supplied as debossed tablets and contain the following coloring agents:

- **50 mg tablets:** red iron oxide, black iron oxide, FD&C Blue #2/indigo carmine aluminum lake
- **100 mg tablets:** yellow iron oxide
- **150 mg tablets:** yellow iron oxide, red iron oxide, black iron oxide
- **200 mg tablets:** FD&C Blue #2/indigo carmine aluminum lake

Manufactured by:
Natco Pharma Limited
Kothur-509228, India

Distributed by:
Breckenridge Pharmaceutical, Inc.
Boca Raton, FL 33487

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

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.

LACOSAMIDE tablets, film coated for oral use 

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 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 \leq 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 (purple), 100 mg (yellow), 150 mg (tan), 200 mg (blue) film-coated tablets (3)

CONTRAINDICATIONS

• None (4)

WARNINGS AND PRECAUTIONS

- Monitor patients for suicidal behavior and ideation (5.1)
- Lacosamide tablets may cause dizziness and ataxia (5.2)
- Cardiac Rhythm and Conduction Abnormalities: ECG before beginning lacosamide tablets, and after lacosamide tablets 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 tablets may cause syncope (5.4)
- Lacosamide tablets should be gradually withdrawn to minimize the potential of increased seizure frequency (5.5)
- Multorgan Hypersensitivity Reactions (5.6)

ADVERSE REACTIONS

• Adjunctive therapy: Most common adverse reactions (\geq 10% and greater than placebo) are diplopia, headache, dizziness, nausea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Breckenridge Pharmaceutical, Inc. at 1-800-367-3395 or www.bpxr.com 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 is indicated in patients 17 years and older with partial-onset seizures as adjunctive therapy.

2. DOSAGE AND ADMINISTRATION

2.1 Dosage for Lacosamide Tablets

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, a gradual withdrawal over at least 1 week is recommended (see warning and precautions (5.5)).

2.2 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 tablets is recommended for patients with severe renal impairment (creatinine clearance (CL_{CR}) less than or equal to 30 mL/min) and in patients with end stage renal disease. Lacosamide tablets are effectively removed from plasma by hemodialysis. Following a 4-hour hemodialysis treatment, dosage supplementation of up to 50% should be considered. In all renally 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 tablets. 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 tablets. 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

- 50 mg (purple), 100 mg (yellow), 150 mg (tan), 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 189 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 16,009 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 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 (5-100 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 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar.

Anyone considering prescribing lacosamide tablets or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which antiepileptics are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts or behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and 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.

5.2 Dizziness and Ataxia

Lacosamide may cause dizziness and ataxia.

In patients with partial-onset seizures taking 1 to 3 concomitant AEDs, dizziness was experienced by 25% of patients randomized to the recommended doses (200 to 400 mg/day) of lacosamide tablets (compared with 9% of placebo patients) and was the adverse event most frequently leading to discontinuation (3%). Ataxia was experienced by 6% of patients randomized to the recommended doses (200 to 400 mg/day) of lacosamide tablets (compared to 2% of placebo patients). The onset of dizziness and ataxia was most commonly observed during titration. There was a substantial increase in these adverse events at doses higher than 400 mg/day (see Adverse Reactions (6.1)).

5.3 Cardiac Rhythm and Conduction Abnormalities

PR interval prolongation

Dose-dependent prolongations in PR interval with lacosamide tablets have been observed in clinical studies in patients and in healthy volunteers (see Clinical Pharmacology (12.3)). In a study 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% (0/564) 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 tablets and 0% (0/291) of patients receiving placebo. Second degree and complete AV block have been reported in patients in pain studies and in patients with lacosamide. When lacosamide is given with other drugs that prolong the PR interval, further PR prolongation is possible.

Lacosamide tablets 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. In patients with structural heart disease, in such patients, obtaining an ECG before beginning lacosamide tablets, and after lacosamide tablets is titrated to steady-state maintenance dose, is recommended.

Atrial fibrillation and Atrial flutter

In the short-term investigational trials of lacosamide tablets in epilepsy patients, there were no cases of atrial fibrillation or flutter. Both atrial fibrillation and atrial flutter were observed in open-label, long-term experience. In patients with diabetic neuropathy, 0.5% of patients treated with lacosamide tablets experienced an adverse reaction of atrial fibrillation or atrial flutter, compared to 0% of placebo-treated patients. Lacosamide tablets administration may predispose to atrial arrhythmias (atrial fibrillation or flutter), especially in patients with diabetic neuropathy and/or cardiovascular disease.

5.4 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 400 mg/day. The cause of syncope was not determined in most cases. However, several were associated with either changes in orthostatic blood pressure, atrial flutter/fibrillation (and associated tachycardia), or bradycardia. Cases of syncope have also been observed in open-label clinical epilepsy studies. These cases were associated with a history of risk factors for cardiac disease and the use of drugs that slow AV conduction.

5.5 Withdrawal of Antiepileptic Drugs (AEDs)

As with all AEDs, lacosamide tablets should be withdrawn gradually (over a minimum of 1 week) to minimize the potential of increased seizure frequency in patients with seizure disorders.

5.6 Multorgan Hypersensitivity Reactions

One case of symptomatic hepatitis and nephritis was observed among 4011 subjects exposed to lacosamide during clinical development. The event occurred in a healthy volunteer, 10 days after stopping lacosamide tablets treatment. The subject was not taking any concomitant medication and potential known viral etiologies for hepatitis were ruled out. The subject fully recovered within a month, without specific treatment. The case is consistent with a delayed multorgan hypersensitivity reaction. Additional potential cases included 2 with rash and elevated liver enzymes and 1 with myocarditis and hepatitis of uncertain etiology. Multorgan hypersensitivity reactions (also known as Drug Reaction with Eosinophilia and Systemic Symptoms, or DRESS) have been reported with other antiepileptics and typically, although not exclusively, present with fever and rash associated with other organ system involvement, that may or may not include eosinophilia, hepatitis, nephritis, lymphadenopathy, and/or myocarditis. Because this disorder is variable in its expression, other organ system signs and symptoms not noted here may occur. If this reaction is suspected, lacosamide tablets should be discontinued and alternative treatment started.

6. ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in the labeling:

- Suicidal Behavior and Ideation (see Warnings and Precautions (5.1))
- Dizziness and Ataxia (see Warnings and Precautions (5.2))
- Cardiac Rhythm and Conduction Abnormalities (see Warnings and Precautions (5.3))
- Syncope (see Warnings and Precautions (5.4))
- Multorgan Hypersensitivity Reactions (see Warnings and Precautions (5.6))

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, 1327 patients received lacosamide in controlled and uncontrolled trials, of whom 1000 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 8% and 17% in patients randomized to receive lacosamide tablets at the recommended doses of 200 and 400 mg/day, respectively, 29% at 600 mg/day, and 5% in patients randomized to receive placebo. The adverse reactions most commonly ($>$ 1% on lacosamide tablets 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 \geq 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					
Contusion	3	3	4	2	3
Skin laceration	2	3	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

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Dimensions (Front - 300 x 640 mm - Back - 300 x 640 mm)

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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 tablets in adult patients with partial-onset seizures who were taking 1 to 3 concomitant anti-epileptic drugs. Elevations of ALT to >3x 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: paraesthesia, 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 tablets. 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 tablets, 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 collagen 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 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.

Oral administration of lacosamide to pregnant rats (20, 70, 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)] $\times 2$ and 1 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 postnatal 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 tablets, 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 collagen 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 tablets in this population.

No lacosamide tablets 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} \leq 30 mL/min) and in patients with end stage renal disease. Lacosamide is effectively removed from plasma by hemodialysis. Dose supplementation 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 tablets use is not recommended in patients with severe hepatic impairment [see *Dosage and Administration* (2.3), *Clinical Pharmacology* (12.3)].

9. DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Lacosamide tablets are a Schedule V controlled substance.

9.2 Abuse

In a human abuse potential study, single doses of 200 mg and 800 mg lacosamide produced euphoria-type subjective responses that differentiated statistically from placebo; at 800 mg, these euphoria-type responses were statistically indistinguishable from those produced by alprazolam, a Schedule IV drug. The duration of the euphoria-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% [5/34]) compared to placebo (0%) and in two pharmacokinetic studies following single and multiple doses of 300-800 mg lacosamide (ranging from 6% [2/33] to 25% [3/12]) compared to placebo (0%). However, the rate of euphoria reported as an adverse event in the lacosamide tablets development program at therapeutic doses was less than 1%.

9.3 Dependence

Abrupt termination of lacosamide in clinical trials with diabetic neuropathic pain patients produced no signs or symptoms that are associated with a withdrawal syndrome indicative of physical dependence. However, psychological dependence cannot be excluded due to the ability of lacosamide to produce euphoria-type adverse events in humans.

10. OVERDOSE

There is limited clinical experience with lacosamide overdose in humans. The highest reported accidental overdose of lacosamide during clinical development was 1,200 mg/day. The types of adverse events experienced by patients exposed to supratherapeutic lacosamide doses during clinical trials were not clinically different from those of patients administered recommended doses of lacosamide. None were fatal.

There has been a single case of intentional overdose in a clinical trial by a patient who self-administered 12,000 mg lacosamide along with large doses of zonisamide, topiramate, and gabapentin. The patient presented in a coma with AV block, generalized tonic-clonic seizures and was hospitalized. An EEG revealed epileptic waveforms. The patient recovered 2 days later.

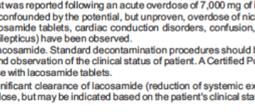
In postmarketing experience, fatal cardiac arrest was reported following an acute overdose of 7,000 mg of lacosamide tablets in a patient with cardiovascular risk factors; however, the case may have been confounded by the potential, but unproven, overdose of nifedipine. In postmarketing reports following single acute overdoses of 1,000 mg or greater of lacosamide tablets, cardiac conduction disorders, decreased level of consciousness, and seizures (generalized tonic-clonic seizures and status epilepticus) have been observed.

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 a patient. A Certified Poison Control Center should be contacted for up to date information on the management of overdose with lacosamide tablets.

Standard hemodialysis procedures result in significant clearance of lacosamide (reduction of systemic exposure by 50% in 4 hours). Hemodialysis has not been performed in the few known cases of overdose, but may be indicated based on the patient's clinical state or in patients with significant renal impairment.

11 DESCRIPTION

The chemical name of lacosamide, the single (R)-enantiomer, is (R)-2-acetamido-N-benzyl-3-methoxypropionamide (IUPAC). Lacosamide is a functionalized amino acid. Its molecular formula is $C_{14}H_{19}NO_3$ and its molecular weight is 250.30. The chemical structure is:



Lacosamide is a white to light yellow powder. It is sparingly soluble in water and slightly soluble in acetonitrile and ethanol.

11.1 Lacosamide tablets

Lacosamide tablets contain the following inactive ingredients: colloidal silicon dioxide, croscopolone, hydroxypropyl cellulose, lecithin, low-substituted hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and eye pigments specified below.

Lacosamide tablets are supplied as debossed tablets and contain the following coloring agents:

50 mg tablets: red iron oxide, black iron oxide, FD&C Blue #2/indigo carmine aluminum lake

100 mg tablets: yellow iron oxide

150 mg tablets: yellow iron oxide, red iron oxide, black iron oxide

200 mg tablets: FD&C Blue #2/indigo carmine aluminum lake

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism by which lacosamide exerts its antiepileptic effects 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 hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing.

12.2 Pharmacodynamics

A pharmacokinetic-pharmacodynamic (efficacy) analysis was performed based on the pooled data from the 3 efficacy trials for partial-onset seizures. Lacosamide exposure is correlated with the reduction in seizure frequency. However, doses above 400 mg/day do not appear to confer additional benefit in group analyses.

Cardiac Electrophysiology

Electrocardiographic effects of lacosamide were determined in a double-blind, randomized clinical pharmacology trial of 247 healthy subjects. Chronic oral doses of 400 and 800 mg/day were compared with placebo and a positive control (400 mg moxifloxacin). Lacosamide did not prolong QTc interval and did not have a dose-related or clinically important effect on QRS duration. Lacosamide produced a small, dose-related increase in mean PR interval. At steady-state, the time of the maximum observed mean PR interval corresponded with C_{max} . The placebo-subtracted maximum increase in PR interval (at C_{max}) was 7.3 ms for the 400 mg/day group and 11.9 ms for the 800 mg/day group. For patients who participated in the controlled trials, the placebo-subtracted mean maximum increase in PR interval for a 400 mg/day lacosamide tablets dose was 3.1 ms in patients with partial-onset seizures and 9.4 ms for patients with diabetic neuropathy.

12.3 Pharmacokinetics

The pharmacokinetics of lacosamide has been studied in healthy adult subjects (age range 18 to 87), adults with partial-onset seizures, adults with diabetic neuropathy, and subjects with renal and hepatic impairment.

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 hours 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. Pharmacokinetics of lacosamide are dose proportional (100-800 mg) and time invariant, with low inter- and intra-subject variability. Compared to lacosamide the major metabolite, O-desmethyl, has a longer $T_{1/2}$ (0.5 to 12 hours) and elimination half-life (15-23 hours).

Absorption and Bioavailability

Lacosamide is completely absorbed after oral administration. The oral bioavailability of lacosamide tablets is approximately 100%. Food does not affect the rate and extent of absorption. After intravenous administration, C_{max} is reached at the end of infusion. The 30- and 60-minute intravenous infusions are bioequivalent to the oral tablet.

In a trial comparing the oral tablet with an oral solution containing 10 mg/mL lacosamide, bioequivalence between both formulations was shown.

Distribution

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.

Metabolism and Elimination

Lacosamide is primarily eliminated from the systemic circulation by renal excretion and biotransformation. After oral and intravenous administration of 100 mg [^{14}C]-lacosamide approximately 95% of radioactivity administered 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, CYP2C9, 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 mildly (Cl_{cr} 50-80 mL/min) and moderately (Cl_{cr} 30-50 mL/min) and 60% in severely (Cl_{cr} \leq 30 mL/min) renally impaired patients compared to subjects with normal renal function (Cl_{cr} \geq 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 tablets 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 50-60% 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 (18-64 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 tablets between CYP2C19 poor metabolizers and extensive metabolizers. Results from a trial in poor metabolizers (PM) (N=4) and extensive metabolizers (EM) (N=8) of cytochrome P450 (CYP) 2C19 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, 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 was not a substrate or inhibitor for P-glycoprotein.

Lacosamide is a substrate of CYP3A4, CYP2C9, and CYP2C19. Patients with renal or hepatic impairment who are taking strong inhibitors of CYP3A4 and CYP2C9 may have increased exposure to lacosamide.

Since <1% 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, clobazepam, and zonisamide were not affected by concomitant intake of lacosamide tablets 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 tablets 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 tablets were co-administered 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 tablets (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 tablets (300 mg single dose). However, plasma levels of the O-desmethyl metabolite were reduced about 60% 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 0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel in healthy subjects, except that a 20% increase in ethinyl estradiol C_{max} was observed.

Warfarin

Co-administration 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 ≥ 2 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 tablets 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).