

Lacosamide

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Generic Name:

LACOSAMIDE

Proprietary Name: *Vimpat* (UCB)

Approval Rating: 1S

Therapeutic Class: Anticonvulsants

Similar Drugs: None

Sound- or Look-Alike Names:

Glucosamide, Loperamide

INDICATIONS

Lacosamide tablets are indicated as adjunctive therapy for partial-onset seizures in patients 17 years of age and older; the injectable is indicated as adjunctive therapy for partial-onset seizures when oral administration is temporarily not feasible in these patients.¹

Lacosamide was also submitted for review by the US Food and Drug Administration (FDA) in the treatment of diabetic neuropathic pain but has not been approved for this indication.^{2,3}

CLINICAL PHARMACOLOGY

The precise mechanism of the anticonvulsant effect of lacosamide has not been fully elucidated.¹ Lacosamide enhances sodium channel slow inactivation and modulates collapsin response mediator protein-2 (CRMP-2).⁴⁻⁶ Lacosamide reduces voltage-gated sodium channel availability by selective enhancement of slow inactivation without interacting with fast-inactivation gating.⁷⁻⁹

Slow inactivation of sodium channels is a mechanism by which neurons reduce stimulated or ectopic hyperactivity. It has been suggested that enhancement of slow inactivation may be a mechanism by which an agent can selectively reduce pathophysiologic activity without having a major influence on physiologic activity.^{7,8} Although lacosamide binds CRMP-2, a phosphoprotein involved in neuronal differentiation and control of axonal outgrowth, the role of CRMP-2 binding in seizure control is not known.¹

Lacosamide does not bind gamma-aminobutyric acidergic or glutamatergic targets and does not modulate calcium or potassium currents.^{10,11} Receptor binding also has not been identified at receptor sites, including adenosine, alpha or beta adrenergic, muscarinic, histamine, dopamine, or serotonin.¹¹

A lacosamide binding site has not been identified, but it is believed that the stereospecific activity of lacosamide (the active R-enantiomer is at least 10-fold more active than the S-enantiomer) suggests the presence of a specific binding site.¹¹ The commercially available tablets and injectable contain only the active R-enantiomer.¹

Observations of lacosamide demonstrated that it protects against partial and generalized seizures in several animal models (maximal electroshock-induced sei-

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zures in mice and rats, rat hippocampal kindling model, sound-induced seizures in genetically susceptible mice, and the 6 Hz model of psychomotor seizures in mice), but it was inactive against clonic seizures induced by chemoconvulsant agents (eg, bicuculline, pentyl-enetetrazol, picrotoxin).^{10,12-16} Lacosamide also antagonized *N*-methyl-D-glucamide-induced seizures in mice and was effective in the homocysteine model of status epilepticus.¹³ Synergistic anticonvulsant effects against 6 Hz-induced seizures have been observed with the combination of lacosamide with carbamazepine, lamotrigine, topiramate, gabapentin, or levetiracetam; additive effects were observed with the combination of lacosamide with phenytoin or valproate.¹² Lacosamide reduced pain behavior in rat models of bone cancer pain, chemotherapy-induced neuropathic pain, diabetic neuropathic pain, central and trigeminal neuropathic pain, muscle pain, and osteoarthritis pain.¹⁷⁻²¹ Lacosamide also has exhibited activity in animal models of essential tremor and tardive dyskinesias.²²⁻²⁶

PHARMACOKINETICS

Oral lacosamide bioavailability is approximately 100%.^{1,4} Peak concentrations are reached within 1 to 5 hours after oral administration and at the end of the intravenous (IV) infusion.^{1,27,28} Administration of oral lacosamide with food does not alter the rate or extent of absorption.^{1,4,29} Bioequivalence has been demonstrated between oral lacosamide 200 mg administered as tablets and IV lacosamide administered as 30- or 60-minute infusions.^{1,30} Lacosamide has low protein binding (less than 15%).⁴ A linear relationship has been observed over a dosage range from 100 to 800 mg/day.^{1,4}

The elimination half-life is approximately 13 hours.^{1,4,27} Steady-state concentrations are reached after 3 days of twice-daily dosing.¹ Elimination is primarily by renal excretion and CYP2C19-mediated metabolism. Approximately 40% of the dose is excreted renally as unchanged drug; about 30% is excreted as the *O*-desmethyl metabolite, and another 20% as a structurally unknown polar fraction.¹ The major metabolite, *O*-desmethyl-lacosamide, is inactive. Peak concentrations of *O*-desmethyl-lacosamide are reached within 0.5 to 12 hours of lacosamide administration. It has an elimination half-life of 15 to 23 hours.¹ Lacosamide concentrations are similar in poor and extensive metabolizers of CYP2C19; however, *O*-desmethyl-lacosamide concentrations are reduced in poor metabolizers.¹

The area under the curve (AUC) of lacosamide was increased by approximately 25% in patients with mild or moderate renal impairment (creatinine clearance [CrCl] of 30 to 80 mL/min) and 60% in patients with severe renal impairment (CrCl of 30 mL/min or less). Peak concentrations were unchanged. Dosage adjustments are recommended for patients with severe renal impairment and patients with end-stage renal disease. Lacosamide is removed from plasma by hemodialysis. Following a 4-hour hemodialysis session, the lacosamide AUC was reduced by approximately 50%. Dose supplementation is recommended following hemodialysis.¹

In patients with moderate hepatic impairment (Child-Pugh class B), the lacosamide AUC was approximately 50% to 60% higher than in healthy patients. Dose adjustments are recommended for patients with mild or moderate hepatic impairment. Use is not rec-

ommended in patients with severe hepatic impairment because lacosamide pharmacokinetics have not been assessed in that population.¹

In patients older than 65 years of age, dose- and body weight-normalized AUC and peak concentration were increased by about 20% compared with younger patients. Dose adjustments are not necessary.¹ Lacosamide pharmacokinetics have not been studied in children.¹ It does not appear that gender and race influence lacosamide pharmacokinetics.¹

COMPARATIVE EFFICACY

Partial-Onset Seizures

The efficacy of lacosamide as adjunctive therapy for partial-onset seizures was primarily established in three 12-week, randomized, double-blind, placebo-controlled, multicenter studies enrolling adult patients. Patients enrolled in these studies had partial-onset seizures with or without secondary generalization that were not adequately controlled on 1 to 3 concomitant antiepileptic agents. Eligibility for study inclusion required that patients experienced an average of 4 or more partial-onset seizures per 28 days with no seizure-free period exceeding 21 days during an 8-week baseline period before randomization. Overall, the patients included in these studies had a mean duration of epilepsy of 24 years and a median baseline seizure frequency ranging from 10 to 17 seizures per 28 days.^{1,31}

Following randomization, doses were titrated to the randomized dose. Lacosamide was initiated at a dosage of 50 mg twice daily and increased in weekly increments of 100 mg/day to the target dosage (200, 400, or 600 mg/day). The titration phase lasted 6 weeks in 2 studies and 4 weeks in 1 study. Following the titration phase, all stud-

ies included a 12-week maintenance phase during which patients continued taking steady doses of study medication. The primary study end point was the reduction in 28-day seizure frequency from baseline.¹

The first study enrolled 418 adults with uncontrolled simple or complex partial-onset seizures with or without secondary generalization. Patients received placebo or lacosamide 200, 400, or 600 mg/day administered in 2 equally divided doses. Lacosamide doses were titrated in weekly increments of 100 mg/day over 6 weeks and maintained for 12 weeks. Most patients in the study (84%) were taking 2 antiepileptic agents when lacosamide therapy was added; the rest were taking 1 other agent when lacosamide was added. Despite treatment with 1 or 2 concomitant antiepileptic agents, the median seizure frequency per 28 days at baseline was 11 to 13. The median percent reduction in seizure frequency per 28 days was 10% with placebo, 26% with lacosamide 200 mg/day, 39% with lacosamide 400 mg/day ($P = 0.0023$), and 40% with lacosamide 600 mg/day ($P = 0.0084$). A 50% reduction in seizure frequency was achieved in 22% of patients receiving placebo, 33% receiving lacosamide 200 mg/day, 41% receiving lacosamide 400 mg/day ($P = 0.0038$), and 38% receiving lacosamide 600 mg/day ($P = 0.0141$). A 75% reduction in seizure frequency was achieved in 6.3% receiving placebo, 11.2% receiving lacosamide 200 mg/day, 22.4% receiving lacosamide 400 mg/day ($P = 0.002$), and 16.2% receiving lacosamide 600 mg/day ($P = 0.0334$). Of all patients in the lacosamide groups, 7 did not experience any seizures throughout the maintenance period. The median change in percentage of seizure-free

days was 3% in the placebo group, 6% in the lacosamide 200 mg/day group, 12% in the lacosamide 400 mg/day group ($P = 0.0036$), and 12% in the lacosamide 600 mg/day group ($P = 0.0004$). Patients in the lacosamide 400 mg/day group experienced greater improvement in quality of life than the patients in the other treatment groups.⁴

The second study enrolled 405 patients with uncontrolled partial-onset seizures taking 1 to 3 concomitant antiepileptic agents. Patients with at least 8 seizures and not more than a 21-day seizure-free period during an 8-week baseline assessment were randomized to therapy with placebo or lacosamide 400 or 600 mg/day (administered twice daily). Lacosamide doses were titrated over 6 weeks in 100 mg/wk increments and maintained for 12 weeks. The median percent reduction in seizure frequency per 28 days was 20.8% with placebo, 37.3% with lacosamide 400 mg/day ($P = 0.0078$), and 37.8% with lacosamide 600 mg/day ($P = 0.0061$). A 50% reduction in seizure frequency was achieved in 18.3% of patients treated with placebo, 38.3% treated with lacosamide 400 mg/day ($P = 0.0004$), and 41.2% treated with lacosamide 600 mg/day ($P = 0.0005$).³²

In the third study, lacosamide 200 and 400 mg/day were assessed in 485 patients with uncontrolled partial-onset seizures taking 1 to 3 concomitant antiepileptic agents. Patients with at least 8 seizures and not more than a 21-day seizure-free period during an 8-week baseline assessment were randomized to placebo or lacosamide given twice daily. Lacosamide doses were titrated over 4 weeks and maintained for 12 weeks. The median percentage reduction in seizure frequency was 21% with placebo, 35% with lacosamide 200 mg/day ($P =$

0.0223), and 36% for lacosamide 400 mg/day ($P = 0.0325$). A 50% reduction in seizure frequency was achieved in 26% in the placebo group, 35% in the lacosamide 200 mg/day group ($P = 0.0735$), and 41% in the lacosamide 400 mg/day group ($P = 0.0063$).³³

In an interim analysis of an extension study enrolling 370 patients previously enrolled in a trial of lacosamide for adjunctive therapy in partial-onset seizures, 76.8% of patients had more than 12 months of lacosamide exposure, 60.5% had more than 24 months of lacosamide exposure, 55.7% had more than 30 months of exposure, and 37.8% had more than 36 months of exposure. Dosages in the range of 100 to 800 mg/day were permitted; the median modal dosage was 400 mg/day, although 30.8% of patients had a median modal dosage of 600 to 800 mg/day. The median reduction from baseline in 28-day seizure frequency was 45.9%. A 50% or greater response to therapy was achieved in 46.6% of patients.^{34,35}

Intravenous lacosamide, as a replacement for oral lacosamide, was assessed in a randomized, double-blind, double-dummy inpatient study enrolling 60 patients with partial-onset seizures participating in an ongoing open-label extension study of oral lacosamide. Following a 1-day screening period in which patients received a single infusion of IV placebo, as well as their twice-daily oral lacosamide dose, patients received IV lacosamide and oral placebo or IV placebo and oral lacosamide for 2 days. Infusions were administered over 60 minutes in the first 30 patients enrolled and over 30 minutes in the next 30 patients enrolled. The safety and tolerability of IV lacosamide were consistent with that of oral lacosamide. Seizure frequency remained stable.³⁰

Intravenous lacosamide, as a replacement for oral lacosamide, also was assessed in an open-label study enrolling 160 patients receiving adjunctive twice-daily oral lacosamide 200 to 800 mg/day. Patients received IV lacosamide twice daily for 2 to 5 days, administered as a 30-minute infusion in 40 patients, a 15-minute infusion in 100 patients, and a 10-minute infusion in 20 patients. A total of 69% of patients received 400 to 800 mg/day. Adverse reactions did not differ with administration times. It did not appear that seizure patterns for individual subjects changed while receiving IV lacosamide.³⁶⁻³⁸

Diabetic Neuropathy

Oral lacosamide was assessed in a randomized, double-blind, placebo-controlled study enrolling 119 patients with pain attributed to diabetic neuropathy and a score of at least 4 on the 11-point Likert pain scale. Patients received placebo or lacosamide titrated from 100 to 400 mg/day or the maximum tolerated dosage. The primary efficacy end point was the change in pain score on the Likert pain scale. Lacosamide provided better pain relief than placebo ($P = 0.039$). Onset of pain relief was observed by the end of the first week on a dosage of 100 mg/day. A 2-point or more reduction in pain score was observed in 36 of 60 (60%) patients taking lacosamide compared with 30 of 59 (50.8%) taking placebo. Improvements also were observed in sleep, general activity, present pain intensity, and the overall visual analog scale (VAS) assessment of pain (Short-Form McGill Pain Questionnaire). Based on VAS pain scores, lacosamide produced a 50% reduction in pain score from baseline to end point compared with a 36% reduction with placebo ($P = 0.0477$). Pain-free days in-

creased to 18.1% with lacosamide compared with 7.5% with placebo. Quality of life (Short-Form-36 [SF-36] Quality of Life Questionnaire) showed greater improvement with lacosamide on pain ($P = 0.022$) and vitality ($P = 0.024$) domains. Both Patient ($P = 0.0159$) and Clinical Global Impression of Change ($P = 0.0493$) ratings favored lacosamide.²⁷ Oral lacosamide was further assessed in 69 patients completing this double-blind study and enrolling in an open-label extension study. Of the 69 patients enrolled, 37 continued in the extension phase of the study for more than 1 year and 34 remained in the study until it was terminated at approximately 2.5 years. The mean duration of lacosamide therapy was 450 days, and the most commonly prescribed dosage was 400 mg/day. The mean reduction in overall Likert pain score/100-mm VAS from baseline to 6, 12, 18, and 24 months was $-3.3/-41$, $-3.4/-37$, $-3.5/-39$, and $-3/-36$, respectively. Pain interference with sleep and activity also was reduced from baseline and maintained through 24 months. Improvement also was observed in the SF-36 Quality of Life scores for the domains of bodily pain ($P < 0.001$), physical functioning ($P = 0.027$), vitality ($P = 0.02$), and social functioning ($P = 0.018$). Of the 34 patients remaining in the study at study termination, 32 opted for continuation with lacosamide therapy in another long-term, open-label study.^{39,40}

Oral lacosamide also was assessed in a randomized, double-blind, placebo-controlled study enrolling 370 patients with moderate-to-severe diabetic neuropathic pain. Patients received placebo or lacosamide 200, 400, or 600 mg/day, with dosages titrated in weekly increments of 100 mg/day and then maintained for 12 weeks. Mean

baseline Likert pain scores ranged from 6.4 to 6.6. The mean reduction in Likert pain score from baseline to the last 4 weeks of maintenance were -1.8 in the placebo group, -2.1 in the lacosamide 200 mg/day group, -2.5 in the lacosamide 400 mg/day group ($P = 0.0126$), and -2.2 in the lacosamide 600 mg/day group. The change in pain score in the 400 mg/day group was significant compared with placebo from week 4 of dose titration through the end of the maintenance phase. Patient global impression of change in pain scores was improved in both the 400 and 600 mg/day groups ($P = 0.02$ vs placebo).^{41,42}

Oral lacosamide was assessed further in a randomized, placebo-controlled study enrolling 469 patients with painful distal diabetic neuropathy. Patients received placebo or lacosamide 200, 400, or 600 mg/day. Lacosamide therapy was titrated to the assigned dose and then maintained for 12 weeks. Mean reductions in pain scores on the Likert scale from baseline to the last 4 weeks of maintenance were -1.67 with placebo, -2.01 with lacosamide 200 mg/day, -2.29 with lacosamide 400 mg/day, and -2.23 with lacosamide 600 mg/day, although the differences were not significant.⁴³

An interim analysis of an ongoing open-label extension study of lacosamide in painful diabetic neuropathy described the experiences of 451 patients. Of the 451 patients included in the open-label extension, 314 (69.6%) were still receiving the drug. The mean duration of exposure was 216 days, with a maximum duration of 516 days. Common dosages were 400 mg/day (26.4%) and 600 mg/day (22%). The mean pain score was 6.35 at baseline and had declined to 2.78 at the end of the titration

phase, 2.16 after 6 months, 2.33 after 12 months, and 2.28 after 18 months in the maintenance phase. More than 95% of patients reported feeling better after 6, 12, and 18 months in the maintenance phase.⁴⁴

Lacosamide 400 mg/day also was compared with placebo in a randomized, double-blind study enrolling 549 patients with diabetic neuropathic pain. Patients were randomized to placebo (179 patients) or lacosamide administered with either a standard 100 mg/week titration (181 patients) or a fast titration reaching the 400 mg/day target dose in 1 week (189 patients). The primary end point was the change in average daily pain score from baseline to the last 4 weeks of maintenance therapy. Standard-titration lacosamide reduced pain scores compared with placebo ($P = 0.04$). Similar pain reductions were reported for standard-titration lacosamide (-2.34 points) and fast-titration lacosamide (-2.12), although results comparing fast titration directly with placebo were not provided. The median days to sustainable pain relief was 10 days with standard-titration lacosamide, 11 days with fast-titration lacosamide, and 31 days with placebo. More patients in the fast-titration group discontinued therapy because of adverse reactions (6.7% with placebo, 8.8% with standard titration, and 15.9% with fast titration). No advantage of a fast-titration schedule was evident in this study.⁴⁵

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

The package insert describes no contraindications to lacosamide therapy.¹

Warnings and Precautions

As with other anticonvulsants, the lacosamide product labeling

contains a warning regarding an increased risk of suicidal behavior and ideation in patients taking these agents for any indication. Patients should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior.¹

Lacosamide may cause dizziness, ataxia, or syncope. Patients should be advised of the risk of these adverse reactions and cautioned not to drive or operate other machinery until they know how lacosamide will affect their ability to perform such activities. Dizziness occurred in 25% of patients receiving lacosamide as adjunctive therapy (compared with 8% of patients receiving placebo) for partial-onset seizures who are taking 1 to 3 concomitant antiepileptic agents. Ataxia was experienced by 6% of patients receiving lacosamide compared with 2% receiving placebo. Dizziness and ataxia were most commonly observed during dose titration. Syncope was observed primarily in patients with diabetic neuropathy who were treated with lacosamide; several cases were associated with orthostatic hypotension, atrial flutter/fibrillation, or bradycardia.¹

Dose-dependent PR interval prolongation has been observed in association with lacosamide. Caution is advised for patients with known cardiac conduction problems (such as marked first-degree atrioventricular [AV] block, second-degree or higher AV block, or sick sinus syndrome without a pacemaker), patients with severe cardiac disease (such as myocardial ischemia or heart failure), and patients taking other drugs known to induce PR interval prolongation. In patients with cardiac conduction problems or severe cardiac disease, an electrocardiogram is recom-

mended before initiating therapy with lacosamide and following titration to steady state.¹

Atrial fibrillation or atrial flutter occurred in 0.5% of patients with diabetic neuropathy treated with lacosamide compared with none treated with placebo. Lacosamide may predispose to atrial arrhythmias, especially in patients with diabetic neuropathy or cardiovascular disease.¹

In patients with seizure disorders, lacosamide should be gradually withdrawn over a minimum of 1 week to minimize the potential of increased seizure frequency.¹ Rapid withdrawal in patients receiving lacosamide in the therapy of painful diabetic neuropathy was not associated with any withdrawal symptoms.⁴⁶

One case of symptomatic hepatitis and nephritis, consistent with a delayed multiorgan hypersensitivity reaction, was observed among 4,011 subjects exposed to lacosamide during clinical development. The event occurred in a healthy volunteer 10 days after stopping lacosamide. The subject was not taking any concomitant medications, and viral causes of hepatitis were ruled out. Additional potential cases included 2 with rash and elevated liver enzymes and 1 with myocarditis and hepatitis of uncertain etiology. Multiorgan hypersensitivity reactions have been reported with other anticonvulsants and usually present with fever and rash plus other organ system involvement that can include eosinophilia, hepatitis, nephritis, lymphadenopathy, and/or myocarditis. If this disorder is suspected, lacosamide therapy should be discontinued.¹

Dose adjustments are recommended in patients with severe renal impairment (CrCl of 30 mL/min or less) and in patients with mild or moderate hepatic

Table 1. Most Common Adverse Reactions With Lacosamide Reported in the Pivotal Clinical Trials for the Treatment of Partial-Onset Seizures¹

<i>Adverse Reactions</i>	<i>Placebo (n = 364)</i>	<i>Lacosamide 200 mg/day (n = 270)</i>	<i>Lacosamide 400 mg/day (n = 471)</i>	<i>Lacosamide 600 mg/day (n = 203)</i>
Dizziness	8%	16%	30%	53%
Nausea	4%	7%	11%	17%
Diplopia	2%	6%	10%	16%
Vomiting	3%	6%	9%	16%
Blurred vision	3%	2%	9%	16%
Fatigue	6%	7%	7%	15%
Ataxia	2%	4%	7%	15%
Headache	9%	11%	14%	12%
Tremor	4%	4%	6%	12%
Nystagmus	4%	2%	5%	10%
Somnolence	5%	5%	8%	8%
Balance disorder	0%	1%	5%	6%
Memory impairment	2%	1%	2%	6%
Diarrhea	3%	3%	5%	4%
Vertigo	1%	5%	3%	4%

impairment. Use is not recommended in patients with severe hepatic impairment. Dose titration should be performed with caution in all patients with renal or hepatic impairment. Patients with coexisting renal and hepatic impairment should be closely monitored during dose titration.¹

The safety and effectiveness of lacosamide has not been established in patients younger than 17 years of age.¹

Lacosamide is in pregnancy category C.¹ Although teratogenic effects have not been observed, lacosamide was associated with increased embryofetal and perinatal mortality and growth deficits in rats following administration during pregnancy. Developmental neurotoxicity also was observed following exposure during a period of postnatal development corresponding to the third trimester of human pregnancy. It has been shown that

lacosamide administered in vitro may interfere with the activity of CRMP-2; potential adverse reactions on central nervous system development have not been ruled out. Lacosamide should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.^{1,47}

Lacosamide and/or its metabolites are excreted in the milk of lactating rats. It is not known whether lacosamide is excreted in human milk. Lacosamide should not be used in a mother who is breastfeeding.¹

ADVERSE REACTIONS

The most common adverse reactions, observed in at least 10% of patients in clinical trials and with greater frequency than placebo, have included dizziness, diplopia, headache, and nausea.¹ Dizziness, nausea, and diplopia appear dose related, occurring with greatest fre-

quency in patients receiving lacosamide 600 mg/day.⁴⁸ Other adverse reactions observed during lacosamide therapy have included abnormal vision, ataxia, fatigue, nystagmus, somnolence, tremor, and vomiting.^{4,27,30,32,41,42} Adverse reactions occurring in at least 5% of patients treated with lacosamide and more frequently with lacosamide than placebo are summarized in Table 1.¹ In addition, injection-site pain has been observed with the IV formulation.³⁰ Liver enzyme elevations have been observed occasionally.^{27,30} Adverse reactions have been observed more frequently at the 600 mg/day dosage.⁴² In clinical trials discontinuation because of an adverse reaction occurred in 8% of patients receiving lacosamide 200 mg/day, 17% receiving lacosamide 400 mg/day, and 29% receiving lacosamide 600 mg/day compared with 5% receiving placebo.¹

DRUG INTERACTIONS

Lacosamide does not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP3A4 and does not inhibit CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP2E1, or CYP3A4/5.¹ In vitro data suggest that there is potential for inhibition of CYP2C19 by lacosamide; however, an inhibitory effect on omeprazole pharmacokinetics was not observed in vivo.¹ Lacosamide is neither a substrate nor an inhibitor of P-glycoprotein.¹

With coadministration lacosamide did not alter the plasma concentrations of carbamazepine, carbamazepine epoxide, clonazepam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine 10-monohydroxy metabolite, phenobarbital, phenytoin, topiramate, valproate, or zonisamide.^{1,4,49,50} Neither valproate nor carbamazepine affected the plasma concentration of lacosamide in healthy patients.⁴ In patients with partial-onset seizures, 15% to 20% reductions in lacosamide plasma concentrations were observed when lacosamide was coadministered with carbamazepine, phenobarbital, or phenytoin.¹

Drug interactions also were not observed between lacosamide and digoxin, metformin, or omeprazole.^{29,51} Lacosamide did not alter the pharmacokinetics or pharmacodynamics of an ethinyl estradiol/levonorgestrel oral contraceptive.²⁹

RECOMMENDED MONITORING

Renal and hepatic function should be assessed before initiating therapy. Patients should be monitored for treatment response (seizure frequency), as well as adverse reactions, during therapy.

DOSING

Lacosamide therapy may be initiated with oral or IV adminis-

tration. The recommended initial dosage is 50 mg twice daily. The dosage may be increased based on clinical response and tolerability at weekly intervals by 100 mg/day given as 2 divided doses to a daily dosage of 200 to 400 mg/day. A dosage of 600 mg/day was not more effective than the 400 mg/day dosage in clinical trials and was associated with a higher incidence of adverse reactions.¹

Intravenous lacosamide therapy can be substituted on an milligram-per-milligram basis for patients who are temporarily unable to receive oral therapy. The injection may be given without further dilution or mixed with a compatible diluent and should be given IV over a period of 30 to 60 minutes.¹

Lacosamide tablets may be taken with or without food.¹

A maximum dosage of 300 mg/day is recommended for patients with severe renal impairment (CrCl of 30 mL/min or less) and for patients with end-stage renal disease.¹ Lacosamide is removed from plasma by hemodialysis; following a 4-hour hemodialysis session, dose supplementation of up to 50% should be considered.¹

A maximum dosage of 300 mg/day is recommended for patients with mild-to-moderate hepatic impairment. Lacosamide is not recommended for patients with severe hepatic impairment.¹

PRODUCT AVAILABILITY AND STORAGE

Lacosamide tablets and injection received FDA approval in October 2008.¹ A New Drug Application for lacosamide syrup was accepted by the FDA in November 2007 but has not yet been approved.^{2,3}

Lacosamide is available as 50, 100, 150, and 200 mg oral tablets and as a 200 mg per 20 mL single-

use vial for IV administration. Lacosamide tablets are supplied in bottles of 60 and 180. The injectable is supplied as 20 mL vials in cartons of 10 vials. All dosage forms should be stored at room temperature (20° to 25°C; 68° to 77°F), with excursions permitted between 15° and 30°C (59° and 86°F).¹

The IV formulation is a 10 mg/mL isotonic solution (pH 3.5 to 5) that is stable at room temperature and can be administered with or without dilution.^{1,30} The injection is physically compatible and chemically stable when mixed with sodium chloride 0.9% injection, dextrose 5% injection, or Ringer's lactate injection and stored in glass or polyvinyl chloride bags at room temperature for at least 24 hours.¹

CONCLUSION

Lacosamide offers a unique alternative for patients with uncontrolled partial seizures. The efficacy data indicate that it can improve seizure control when used as adjunctive therapy. It appears that the drug is well tolerated, although additional adverse reaction data are necessary before lacosamide can be recommended as a first-line agent. The apparent lack of drug interactions is a significant advantage for this adjunctive therapy.

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Continuing Education Case Study Quiz

Goal—The goal of this program is to educate the pharmacist about the use of lacosamide in the management of seizures.

Objectives—At the completion of this program, the reader will be able to:

1. Describe the pharmacology and pharmacokinetics of lacosamide.
2. Discuss the risks associated with the use of lacosamide.
3. Discuss the potential benefit of lacosamide for an individual patient.
4. Apply the information on the use of lacosamide to a case study.

Key Words—anticonvulsants, lacosamide, new drugs, seizure

1. **Lacosamide is indicated for:**
 - A. monotherapy treatment of tonic-clonic seizures in children 4 years of age and younger.
 - B. monotherapy treatment of tonic-clonic seizures in adults 17 years of age and older.
 - C. adjunctive treatment of partial-onset seizures in children 4 years of age and younger.
 - D. adjunctive treatment of partial-onset seizures in adults 17 years of age and older.
2. **Lacosamide:**
 - A. binds to the gamma-aminobutyric acid A receptor, which decreases neuronal activity.
 - B. enhances sodium channel slow inactivation and modulates collapsin response mediator protein-2.
 - C. acts on kainate and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors to inhibit excitatory neurotransmission.
 - D. binds to synaptic vesicle glycoprotein 2A, impeding nerve conduction across synapses.
3. **Lacosamide interacts with which of the following receptors?**
 - A. Adenosine
 - B. Muscarinic
 - C. Alpha and beta adrenergic
 - D. None of the above
4. **Oral lacosamide bioavailability is approximately:**
 - A. 25%.
 - B. 50%.
 - C. 75%.
 - D. 100%.
5. **The time to peak concentration following oral administration of lacosamide is:**
 - A. 1 to 5 hours.
 - B. 5 to 9 hours.
 - C. 9 to 13 hours.
 - D. 13 to 17 hours.
6. **The elimination half-life of lacosamide is:**
 - A. 7 hours.
 - B. 9 hours.
 - C. 11 hours.
 - D. 13 hours.
7. **Lacosamide metabolism is primarily:**
 - A. CYP2C19 mediated.
 - B. via conjugation with glucuronic acid.
 - C. via hydrolysis by carboxylesterases.
 - D. via reduction.

Case History

ET is a 65-year-old woman with a history of partial-onset seizures. She is currently taking levetiracetam 500 mg twice daily, but her seizures are not adequately controlled and her doctor wants to start oral lacosamide. ET weighs 115 pounds and her height is 62 inches. Her serum creatinine is 1.8 mg/dL. (Answer questions 8 through 13 regarding ET's case history.)

8. **What is the recommended initial dose of lacosamide for ET?**
 - A. 25 mg twice daily
 - B. 50 mg twice daily
 - C. 75 mg twice daily
 - D. 100 mg twice daily
9. **Should ET's renal function be taken into consideration when dosing lacosamide?**
 - A. No, dosage adjustments are not necessary for patients with severe renal impairment (creatinine clearance less than 30 mL/min).
 - B. No, ET does not have significant renal impairment.
 - C. No, lacosamide only should be adjusted with severe hepatic impairment.
 - D. Yes, dosage restrictions are recommended in severe renal impairment.

10. The maximum dose of lacosamide for ET should be:
 A. 200 mg/day.
 B. 300 mg/day.
 C. 400 mg/day.
 D. 500 mg/day.
11. What is a labeled contraindication to lacosamide use for ET?
 A. Atrial fibrillation
 B. Congestive heart failure
 C. Second-degree or higher atrioventricular block
 D. There are no labeled contraindications to lacosamide therapy.
12. After a week, ET's doctor wants to increase her dose of lacosamide. What is the appropriate dose titration for ET?
 A. Increase by 50 mg/day at weekly intervals
 B. Increase by 100 mg/day at weekly intervals
 C. Increase by 150 mg/day at weekly intervals
 D. Increase by 200 mg/day at weekly intervals
13. The levetiracetam ET is already taking:
 A. is not expected to interact with lacosamide.
 B. will decrease plasma lacosamide concentrations.
 C. will increase plasma lacosamide concentrations.
 D. has an unknown affect on lacosamide concentrations.
14. The most common side effects of lacosamide are:
 A. diarrhea and lupuslike syndrome.
 B. headache and nausea.
 C. rash and ataxia.
 D. somnolence and constipation.
15. Lacosamide is available as:
 A. a suspension and a tablet.
 B. a rapidly dissolving tablet and a film-coated tablet.
 C. an oral solution and an injection.
 D. a tablet and an injection.

Drug Evaluation: Lacosamide
ACPE # 071-999-09-007-H01-P
0.15 CEU

Activity Type: Knowledge based
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Examination Answer Form

Please circle your answers—one answer per question.

- | | |
|------------|-------------|
| 1. A B C D | 9. A B C D |
| 2. A B C D | 10. A B C D |
| 3. A B C D | 11. A B C D |
| 4. A B C D | 12. A B C D |
| 5. A B C D | 13. A B C D |
| 6. A B C D | 14. A B C D |
| 7. A B C D | 15. A B C D |
| 8. A B C D | |



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PROGRAM EVALUATION

Please rate our continuing education offering by responding to the following questions.

1. How well were the learning objectives covered by this activity?

This program described the pharmacology and pharmacokinetics of lacosamide. Completely Fairly well Not at all

The program discussed the risks associated with the use of lacosamide. Completely Fairly well Not at all

After this program, I was able to discuss the potential benefit of lacosamide. Completely Fairly well Not at all

I was able to apply the knowledge from this educational program and other resources to answer questions associated with the case study. Completely Fairly well Not at all

2. The continuing education quiz questions required application of the information. Agree Disagree

3. The content of this article was relevant to the practice of pharmacy. Agree Disagree

4. My personal objectives in participating in this program were fulfilled. Agree Disagree

5. The program increased my knowledge of the subject area. Agree Disagree

6. I will be able to apply aspects of this program to my practice. Agree Disagree

7. The content of this article was scientifically sound. Agree Disagree

8. The article provided a balanced view of the product. Agree Disagree

9. The material was free of commercial bias. Agree Disagree

10. How long did it take you to complete this continuing education program? _____ hours

11. What other continuing education programs or topics would you like to see?

