

# PEDIATRIC PHARMACOTHERAPY

A Monthly Newsletter for Health Care Professionals from the  
University of Virginia Children's Hospital

---

Volume 17 Number 7

July 2011

---

## Lacosamide for the Treatment of Seizures in Children

*Marcia L. Buck, Pharm.D., FCCP, FPPAG*

Lacosamide was approved by the Food and Drug Administration (FDA) on October 28, 2008 for use as adjunctive therapy in adults with partial-onset seizures.<sup>1,2</sup> Its unique mechanism of action, the lack of significant drug interactions, and generally mild adverse effect profile have made lacosamide a useful addition to treatment with traditional antiepileptics.<sup>3,4</sup> While not yet approved for use in children, preliminary reports suggest it may also be beneficial in pediatric patients. This issue of *Pediatric Pharmacotherapy* will provide an overview of lacosamide and the results of several papers describing its use in children.

### Mechanism of Action

The mechanism of action of lacosamide, (R)-2-acetamido-N-benzyl-3-methoxypropionamide, has not been fully defined. It is a functionalized amino acid that selectively enhances slow inactivation of voltage-gated sodium channels (VGSCs), increasing the proportion of sodium channels unavailable for depolarization. This produces stabilization of neuronal membranes and inhibition of sustained repetitive neuronal firing. Unlike other antiepileptics, including carbamazepine, felbamate, lamotrigine, oxcarbazepine, phenytoin, and topiramate, lacosamide does not alter fast inactivation of VGSCs.

Lacosamide also interacts with collapsin-response mediator protein 2 (CRMP-2). This protein is part of a signal transduction cascade of neurotrophic factors involved in neuronal differentiation, regulation of gene expression, polarization, and axonal outgrowth.<sup>1-4</sup> It has been proposed that binding at CRMP-2 may produce a neuroprotective effect, reducing glutamate-induced excitotoxicity and enhancing the clinical efficacy of lacosamide.<sup>5</sup>

### Pharmacokinetics

Lacosamide is completely absorbed after oral administration, with a bioavailability of

approximately 100%. Food does not alter the rate or extent of absorption. Maximum serum concentrations occur 1-4 hours after an oral dose. The volume of distribution of lacosamide is approximately 0.6 L/kg. It is not highly bound to serum proteins (15%).<sup>3,4</sup>

Approximately 40% of a lacosamide dose is excreted as unchanged drug. Conversion to O-desmethyl-lacosamide via cytochrome P450 2C19 (CYP2C19) accounts for another 20 to 30%. Other metabolites make up the remainder. The O-desmethyl metabolite is not pharmacologically active. The elimination half-life of lacosamide in adults is approximately 13 hours. The pharmacokinetic profile of lacosamide has not been studied in children to date.<sup>3,4</sup>

Area under the concentration curve (AUC) increases by 25% in patients with mild to moderate renal impairment and 60% in those with severe renal impairment. Moderate hepatic impairment increases the AUC by approximately 50 to 60%. Genetic polymorphism (CYP2C19 extensive or poor metabolizers) does not appear to produce clinically significant changes in lacosamide pharmacokinetics.<sup>3,4</sup>

### Case Studies and Clinical Trials

In randomized controlled trials conducted in adults, lacosamide has demonstrated significant benefit in treating refractory seizures, with 30-40% of patients achieving a  $\geq 50\%$  reduction in seizure frequency at doses of 400-600 mg/day. Three case series have been published this year describing the use of lacosamide in children with refractory partial-onset seizures.<sup>6-8</sup>

In April, Gavatha and colleagues at Pendeli Children's Hospital in Athens, Greece reported a series of 18 children (ages 3-18 years) treated with oral lacosamide for at least 3 months.<sup>6</sup> The average treatment duration was 8 months at the time of assessment. All of the children had been

treated with multiple antiepileptics. The average number of previously failed therapies was 7 drugs, with a range from 3 to 16. Lacosamide was initiated at 1 mg/kg/day and increased in 1 mg/kg increments on a weekly basis. Final doses ranged from 2 to 10 mg/kg/day. Thirty-six percent of the children experienced a  $\geq 50\%$  reduction in seizure frequency at first assessment, and 20% maintained this level of seizure control at their second assessment. One year after enrollment, only four of the original 18 children were still on therapy. Lacosamide was discontinued in 12 patients due to lack of efficacy or loss of efficacy during the study. One patient was lost to follow-up. Only one patient discontinued therapy due to an adverse effect. Mild adverse effects were common, however, with 39% of children experiencing symptoms such as somnolence or irritability. Although effective seizure control was not maintained in most patients, the authors concluded that lacosamide still has the potential to be a useful addition to the management of refractory partial-onset seizures in children.

Guilhoto and colleagues of Boston Children's Hospital published their experience with 16 children treated with lacosamide in the June issue of *Pediatric Neurology*.<sup>7</sup> The patients (8-21 years of age) were receiving a median of two other antiepileptics for their refractory partial-onset seizures at the time lacosamide was initiated. Three had undergone epilepsy surgery, nine received vagus nerve stimulation, and three were on a ketogenic diet. The average lacosamide dose was 4.7 mg/kg/day (275 mg/day). Median seizure frequency was 57 per month at baseline and 12.5 per month at follow-up (a 39.6% reduction,  $p < 0.01$ ). Six children (37.5%) had a  $\geq 50\%$  reduction in seizure frequency. Seven patients had no improvement. Four patients discontinued therapy because of adverse effects (tics, behavioral changes, increased seizures, or depression). As with the previous case series, the authors suggested that lacosamide may play a useful role in treating refractory seizures in children and should be evaluated in a prospective controlled trial.

In a third paper, Shiloh-Malawsky and colleagues at the University of North Carolina described an 8-year-old boy with prolonged status epilepticus that was stopped by lacosamide.<sup>8</sup> The patient developed convulsive seizures following a febrile illness and was initially treated with lorazepam and phenytoin, without improvement. The addition of phenobarbital, valproic acid, and levetiracetam did not improve clinical seizure activity or EEG findings. Propofol produced burst suppression initially, but seizures eventually recurred. Upon transfer to the authors' institution, a variety of

antiepileptics were tried over a 10-week period, as well as a ketogenic diet, corticosteroids, IV immune globulin, plasmapheresis, folinic acid, carnitine, and biotin, without benefit. At the time of lacosamide initiation, the patient was receiving six antiepileptics but was still having over 300 partial-onset electrographic seizures per day. Lacosamide was started at a dose of 25 mg twice daily. Within 3 days, seizure frequency had declined significantly. Complete seizure resolution occurred on day 5. The authors concluded that although a direct causal effect could not be proven, a temporal relationship between lacosamide introduction and the reduction in seizure frequency suggests that this drug may have a role in treating refractory status epilepticus.

The manufacturer of lacosamide is currently conducting a Phase II multicenter, open-label study of the safety and pharmacokinetics of lacosamide in children with partial-onset seizures. Children between 1 month and 17 years of age who are still experiencing seizures on stable doses of up to three other antiepileptics will be enrolled. Study subjects will receive lacosamide oral solution in doses of 8, 10, or 12 mg/kg/day for up to 42 days. The estimated study completion date is March 2013.

Another study is currently underway of the safety of IV lacosamide in children ages 4-20 years. This study, being conducted at Le Bonheur Children's Medical Center, will utilize doses of 0.7 to 2.9 mg/kg, up to a maximum of 200 mg. Details for both the Phase II study and this study of IV lacosamide are available on the clinical trials website of the National Institutes of Health ([www.clinicaltrials.gov](http://www.clinicaltrials.gov), accessed 6/13/11).

Not all case studies have shown beneficial results with the addition of lacosamide in children and adults with refractory seizures. Cuzzola and colleagues described three young adult patients (24-27 years of age) in their practice with Lennox-Gastaut syndrome who experienced worsening of their seizure frequency after initiation of lacosamide.<sup>9</sup> All three patients had been initiated on 50 mg/day with increases of 50 mg/day each week. Two of the patients were titrated up to a dose of 200 mg/day, one experienced increased seizures at 15 days and the other at 30 days from the time of the last increase. The third patient developed an increase in seizure frequency 4 days after reaching a dose of 100 mg/day. All patients returned to their baseline seizure frequency after lacosamide was discontinued. The authors hypothesized that this worsening of seizure frequency may reflect an additive or synergistic effect of lacosamide with their patient's other antiepileptic drugs that block VCSGs.

### Precautions

The interaction of lacosamide with CRMP-2, a protein known to be involved in neuronal differentiation and control of axonal outgrowth, may adversely affect central nervous system development. CRMP-2 is known to be highly expressed during gestation and early in life. Studies in rats given lacosamide early in life resulted in decreased brain weight and long-term deficits in learning and memory. Additional research in this area is needed to clarify the risk to benefit ratio of using this therapy in infants and young children, as well as during pregnancy and lactation. Clinicians are encouraged to enroll any pregnant women taking lacosamide into the UCB AED Pregnancy Registry by calling 1-888-233-2334 or going to the product website at [www.vimpat.com](http://www.vimpat.com).<sup>3</sup>

Hypersensitivity reactions to lacosamide appear to be rare, but have been reported. One adult patient enrolled in a Phase III clinical trial experienced acute hepatitis and nephritis consistent with a multiorgan hypersensitivity reaction (also known as drug reaction with eosinophilia and systemic symptoms or DRESS) 10 days after stopping lacosamide. The patient recovered without sequelae. Two other cases of rash with concurrent increased serum transaminases have been reported, as well as a patient who developed myocarditis and hepatitis after starting lacosamide.<sup>3,4</sup>

In clinical trials, lacosamide was found to produce a small, dose-related increase in the PR interval during routine electrocardiographic (ECG) monitoring in a small number of patients. The observed increase was proportional to the dose, with a maximum increase of 7.3 ms in patients taking 400 mg/day and 11.9 ms in those taking 800 mg/day. First degree atrioventricular block was reported in 0.4% of adults in premarketing clinical trials. Lacosamide should be used with caution in patients with cardiac conduction problems or severe cardiac disease. In these patients, an ECG should be obtained prior to starting therapy and at the end of dose titration. Concurrent administration of other drugs that prolong the PR interval should be avoided.<sup>3,4</sup>

Although not reported in lacosamide to date, suicidal thoughts have been described in patients taking other AEDs. In order to educate patients and their families about this risk, the FDA has approved a REMS (risk evaluation and mitigation strategy) program for all of the drugs in this therapeutic class. A Medication Guide must be given to the patient or family at the time any AED is dispensed.<sup>3,4</sup>

Lacosamide oral solution contains aspartame and should be used with caution in patients with phenylketonuria. A 200 mg dose of the oral solution (20 mL) provides 0.32 mg phenylalanine.

At high doses (800 mg or greater), lacosamide can produce a mild euphoria. As a result of the risk for abuse, it was approved as a schedule V controlled substance. The euphoria is not typically seen with antiepileptic doses and in clinical trials, abrupt discontinuation produced no signs of withdrawal.<sup>3,4</sup>

### Adverse Effects

Lacosamide is generally well tolerated. In pooled data from placebo-controlled clinical trials in adults, the most frequent reactions were dizziness (31% vs. 8% in controls), headache (13% vs. 9%), nausea (11% vs. 4%), diplopia (11% vs. 2%), fatigue (9% vs. 6%), vomiting (9% vs. 3%), ataxia (8% vs. 2%), blurred vision (8% vs. 3%), somnolence (7% vs. 5%), and tremor (7% vs. 4%). Most of these adverse effects are dose-related. Discontinuation of lacosamide as the result of an adverse effect has been reported in 8% of adults receiving a dose of 200 mg/day, 17% of those taking 400 mg/day, and 29% of patients taking 600 mg/day.

Elevations in alanine transaminase up to three times the upper limit of normal were reported in 0.7% of patients receiving lacosamide in premarketing trials. These changes have resolved with discontinuation of therapy. Intravenous administration of lacosamide has been associated with injection site pain or discomfort in 2.5% of patients, venous irritation in 1%, and erythema in 0.5%.<sup>1-4</sup>

### Drug Interactions

At this time, no clinically significant drug interactions with lacosamide have been identified. A small (20%) increase in ethinyl estradiol has been reported in women taking lacosamide with oral contraceptives. Minor reductions in serum concentrations (< 20%) occur in carbamazepine, phenytoin, and phenobarbital when given with lacosamide.<sup>3,4</sup>

Novy and colleagues recently reported a series of seven patients who developed neurologic adverse effects after lacosamide was added to a regimen containing other VGSC-blocking antiepileptics.<sup>10</sup> There was no evidence of a pharmacokinetic drug interaction or elevated serum drug concentrations in these patients which might have explained the increased incidence of diplopia, dizziness, and drowsiness. Reduction in the patient's original antiepileptic resulted in symptomatic improvement in all of the cases. As in the paper by Cuzzola<sup>9</sup>, the authors propose

that this apparent pharmacodynamic drug interaction was the result of synergistic VGSC blockade.

#### Availability and Dosing Recommendations

Lacosamide (Vimpat<sup>®</sup>) is available in 50 mg, 100 mg, 150 mg, and 200 mg tablets, a 200 mg/20 mL injectable solution, and a 10 mg/mL strawberry-flavored oral solution. The oral solution must be discarded after 7 weeks from the date of opening.<sup>3</sup>

The recommended initial dose of lacosamide in adults is 50 mg administered twice daily, with weekly titration by 100 mg/day increments. The usual maintenance dose for adults is 200 to 400 mg/day. In clinical trials, increasing the daily dose to 600 mg did not provide greater seizure control, but was associated with a higher incidence of adverse effects.<sup>3,4</sup> There are no clear dosing recommendations for lacosamide in children at this time. Based on the preliminary reports available to date, a starting dose of 1 mg/kg/day, divided and given in two doses, may be considered for initiation of therapy.

No dosage adjustment is needed for mild to moderate renal impairment. In adults with severe renal impairment or end-stage renal disease, the manufacturer recommends a maximum daily dose of 300 mg/day. No dosing guidelines are available for pediatric patients with renal impairment. Lacosamide is removed by hemodialysis. It is recommended that a supplemental dose of up to 50% of the maintenance dose be administered after a 4-hour hemodialysis session. A maximum daily dose of 300 mg/day is also recommended for adults with mild to moderate hepatic impairment. Lacosamide is not recommended for use in patients with severe hepatic impairment.<sup>3,4</sup>

The IV and oral doses of lacosamide are equivalent. Patients being converted from oral to IV therapy should receive their usual oral dose twice daily. Intravenous doses should be infused, with or without further dilution, over 30 to 60 minutes. Lacosamide tablets or solution may be taken with or without food.<sup>3,4</sup>

#### Summary

Lacosamide has the potential to become a useful adjunct in children with seizures refractory to traditional antiepileptics. Preliminary case series and retrospective studies have documented improved seizure control with relatively mild adverse effects. The clinical trials currently underway will soon provide more information on the efficacy and safety of lacosamide in children and allow clinicians to determine the appropriate place of this agent in treatment.

#### **References**

1. Chu-Shore CJ, Thiele EA. New drugs for pediatric epilepsy. *Semin Pediatr Neurol* 2010;17:214-23.
2. Chung SS. Lacosamide: new adjunctive treatment option for partial-onset seizures. *Expert Opin Pharmacother* 2010;11:1595-602.
3. Vimpat<sup>®</sup> prescribing information. UCB, Inc., April 2011. Available at [www.vimpat.com](http://www.vimpat.com) (accessed 6/17/11).
4. Lacosamide. Drug Facts and Comparisons 4.0. Efacts [online]. 2011. Available from Wolters Kluwer Health, Inc. (accessed 6/17/11).
5. Hensley K, Venkova K, Christov A, et al. Collapsin response mediator protein-2: an emerging pathologic feature and therapeutic target for neurodegenerative diseases. *Mol Neurobiol* 2011;43:180-91.
6. Gavatha M, Ionnou I, Papavasiliou AS. Efficacy and tolerability of oral lacosamide as adjunctive therapy in pediatric patients with pharmacoresistant focal epilepsy. *Epilepsy Behav* 2011;20:691-3.
7. Guilhoto LMFF, Loddenkemper T, Gooty VD, et al. Experience with lacosamide in a series of children with drug-resistant focal epilepsy. *Pediatr Neurol* 2011;44:414-9.
8. Shiloh-Malawsky Y, Fan Z, Greenwood R, et al. Successful treatment of childhood prolonged refractory status epilepticus with lacosamide. *Seizure* 2011, doi:10.1016/j.seizure.2011.03.005 (E pub ahead of print).
9. Cuzzola A, Ferlazzo E, Italiano D, et al. Does lacosamide aggravate Lennox-Gastaut syndrome? Report on three consecutive cases. *Epilepsy Behav* 2010;19:650-1.
10. Novy J, Patsalos PN, Sander JW, et al. Lacosamide neurotoxicity associated with concomitant use of sodium channel-blocking antiepileptic drugs: a pharmacodynamic interaction? *Epilepsy Behav* 2011;20:20-3.

#### Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee in June:

1. Fosaprepitant (Emend<sup>®</sup>) was added to the Formulary for the prevention of chemotherapy-induced nausea.
2. Ipilimumab (Yervoy<sup>™</sup>) was added for the treatment of unresectable or metastatic melanoma.
3. Sipuleucel-T (Provenge<sup>®</sup>) was added for the treatment of prostate cancer.
4. The restrictions on bevacizumab (Avastin<sup>™</sup>) were amended to include use in retinopathy of prematurity. It is otherwise restricted to the FDA-approved indications: recurrent ovarian cancer and intravitreal use for macular degeneration, macular edema, or neovascularization.
5. Porfimer sodium (Photofrin<sup>®</sup>) was deleted.

*Contributing Editor: Marcia Buck, Pharm.D.*

*Editorial Board: Kristi N. Hofer, Pharm.D.*

*Michelle W. McCarthy, Pharm.D., FASHP*

*Susan B. Cogut, Pharm.D.*

*If you have comments or suggestions for future issues, please contact us at Box 800674, UVA Health System, Charlottesville, VA 22908 or by e-mail to [mlb3u@virginia.edu](mailto:mlb3u@virginia.edu). This newsletter is also available at <http://www.medicine.virginia.edu/clinical/departments/pediatrics/education/pharmnews>*