

# Apnea Linked to Retinopathy and Neuropathy

BY SHERRY BOSCHERT

FROM THE ANNUAL SCIENTIFIC SESSIONS OF THE AMERICAN DIABETES ASSOCIATION

SAN DIEGO – Obstructive sleep apnea in patients with type 2 diabetes predicted a three- to fourfold higher risk for diabetic peripheral neuropathy or sight-threatening retinopathy, separate analyses have found.

The results suggest that obstructive sleep apnea may play a role in the development of peripheral neuropathy and sight-threatening retinopathy in people with diabetes, Dr. Abd Tahrani and his associates reported at the meeting. Ongoing studies are exploring possible mechanisms involved.

Further study is warranted on the possibility that treating obstructive sleep apnea might affect the development or pro-

gression of retinopathy or neuropathy, added Dr. Tahrani of the University of Birmingham (England), where he is a research fellow for the U.K. National Institute for Health Research.

The prospective studies recruited random patients from a hospital-based, outpatient diabetes clinic in the United Kingdom. Subjects were excluded if they had a known respiratory disorder, including obstructive sleep apnea. Patients had a

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

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

Oral administration of lacosamide to pregnant rats (20, 75, or 200 mg/kg/day) and rabbits (6.25, 12.5, or 25 mg/kg/day) during the period of organogenesis did not produce any teratogenic effects. However, the maximum doses evaluated were limited by maternal toxicity in both species and embryofetal death in rats. These doses were associated with maternal plasma lacosamide exposures [area under the plasma-time concentration curve; (AUC)]  $\approx 2$  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 post-natal developmental toxicity in rats (70 mg/kg/day) was associated with a maternal plasma lacosamide AUC approximately equal to that in humans at the MRHD.

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

#### Pregnancy Registry

UCB, Inc. has established the UCB AED Pregnancy Registry to advance scientific knowledge about safety and outcomes in pregnant women being treated with VIMPAT. To ensure broad program access and reach, either a healthcare provider or the patient can initiate enrollment in the UCB AED Pregnancy Registry by calling 1-888-537-7734 (toll free).

Physicians are also advised to recommend that pregnant patients taking VIMPAT enroll in the North American Antiepileptic Drug 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/>.

#### Labor and Delivery

The effects of VIMPAT 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.

#### Nursing Mothers

Studies in lactating rats have shown that lacosamide and/or its metabolites are excreted in milk. It is not known whether VIMPAT 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 VIMPAT, taking into account the importance of the drug to the mother.

#### Pediatric Use

The safety and effectiveness of VIMPAT in pediatric patients <17 years have not been established.

Lacosamide has been shown *in vitro* to interfere with the activity of CRMP-2, a protein involved in neuronal differentiation and control of axonal outgrowth. Potential adverse effects on CNS development can not 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.

#### Geriatric Use

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

In healthy subjects, the dose and body weight normalized pharmacokinetic parameters AUC and  $C_{max}$  were approximately 20% higher in elderly subjects compared to young subjects. The slightly higher lacosamide plasma concentrations

in elderly subjects are possibly caused by differences in total body water (lean body weight) and age-associated decreased renal clearance. No VIMPAT dose adjustment based on age is considered necessary. Caution should be exercised for dose titration in elderly patients.

#### Patients with Renal Impairment

A maximum dose of 300 mg/day is recommended for patients with severe renal impairment ( $CL_{CR} \leq 30$  mL/min) and in patients with endstage renal disease. VIMPAT is effectively removed from plasma by hemodialysis. Following a 4-hour hemodialysis treatment, AUC of VIMPAT is reduced by approximately 50%. Therefore dosage supplementation of up to 50% following hemodialysis should be considered. In all renal impaired patients, the dose titration should be performed with caution. [see *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)* in Full Prescribing Information]

#### Patients with Hepatic Impairment

Patients with mild to moderate hepatic impairment should be observed closely during dose titration. A maximum dose of 300 mg/day is recommended for patients with mild to moderate hepatic impairment. The pharmacokinetics of lacosamide has not been evaluated in severe hepatic impairment. VIMPAT use is not recommended in patients with severe hepatic impairment [see *Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3)* in Full Prescribing Information]. Patients with co-existing hepatic and renal impairment should be monitored closely during dose titration.

#### DRUG ABUSE AND DEPENDENCE

##### Controlled Substance

VIMPAT is a Schedule V controlled substance.

##### 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 VIMPAT development program at therapeutic doses was less than 1%.

##### 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.

#### OVERDOSAGE

##### Signs, Symptoms, and Laboratory Findings of Acute Overdose in Humans

There is limited clinical experience with VIMPAT overdose in humans. The highest reported accidental overdose of VIMPAT during clinical development was 1200 mg/day which was non-fatal. The types of adverse events experienced by patients exposed to supratherapeutic doses during the trials were not clinically different from those of patients administered recommended doses of VIMPAT.

There has been a single case of intentional overdose by a patient who self-administered 12 grams VIMPAT along with large doses of zonisamide, topiramate, and gabapentin. The patient presented in a coma and was hospitalized. An EEG revealed epileptic waveforms. The patient recovered 2 days later.

##### Treatment or Management of Overdose

There is no specific antidote for overdose with VIMPAT. Standard decontamination procedures should be followed. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of patient. A Certified Poison Control Center should be contacted for up to date information on the management of overdose with VIMPAT.

Standard hemodialysis procedures result in significant clearance of VIMPAT (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.

#### PATIENT COUNSELING INFORMATION

See FDA-approved Medication Guide and Patient Counseling Information section in the Full Prescribing Information.

VIMPAT tablets, VIMPAT injection and VIMPAT oral solution



VIMPAT® is a registered trademark under license from Harris FRC Corporation and covered by one or more claims of U.S. Patent 38,551.

© 2011 UCB, Inc. All rights reserved. Printed in U.S.A. • VE198-0511

04/2011 UCB, Inc.



#### VITALS

**Major Finding:** In adults with diabetes, the presence of obstructive sleep apnea predicted a 3.6-fold greater risk for sight-threatening retinopathy and a threefold greater risk for diabetic peripheral neuropathy, compared with patients without obstructive sleep apnea.

**Data Source:** Two separate prospective, observational cross-sectional studies of 224 patients in the retinopathy study and 231 patients in the neuropathy study who were recruited from a hospital-based, outpatient diabetes clinic.

**Disclosures:** Dr. Tahrani reported having no conflicts of interest.

mean age of 59 years and a mean 11-year history of diabetes, and 48% were white. They underwent one night of home-based multichannel respiratory monitoring and were considered to have obstructive sleep apnea if they had an apnea-hypopnea index of at least 5 events per hour.

In 224 patients who also were assessed for sight-threatening retinopathy, 63% had obstructive sleep apnea and 38% had sight-threatening retinopathy. Patients with obstructive sleep apnea were significantly more likely to have sight-threatening retinopathy (48%) than were patients without obstructive sleep apnea (20%).

The study defined sight-threatening retinopathy as the presence of preproliferative or proliferative retinopathy, maculopathy, or the need for laser treatment.

After adjustment for possible confounders, patients with obstructive sleep apnea were 3.6 times more likely to have sight-threatening retinopathy, 5 times more likely to have advanced diabetic retinopathy, and 4.4 times more likely to have maculopathy than were patients without obstructive sleep apnea.

In a separate study by the same researchers of 231 patients assessed for obstructive sleep apnea and peripheral neuropathy, 65% had obstructive sleep apnea and 45% had diabetic peripheral neuropathy. Patients with obstructive sleep apnea reported more neuropathic symptoms. Among patients with obstructive sleep apnea, 60% had diabetic peripheral neuropathy, compared with 27% of patients without sleep apnea.

Obstructive sleep apnea conferred a significant threefold higher risk for peripheral neuropathy after adjustment for potentially confounding variables, Dr. Tahrani reported. The severity of peripheral neuropathy correlated with the severity of obstructive sleep apnea.

Obstructive sleep apnea was prevalent in 75% and 52% of white and South Asian patients, respectively. Likewise, diabetic peripheral neuropathy was more prevalent in whites (56% vs. 40%). Both differences were significant.

The lower prevalence of obstructive sleep apnea in the South Asian patients might be one reason for the lower prevalence of diabetic peripheral neuropathy, the investigators suggested. ■