

# Channel Mutation Implicated in Neuropathies

BY JEFF EVANS

FROM ANNALS OF NEUROLOGY

**M**utations in the voltage-gated sodium channel  $Na_v1.7$  appear to be the source of chronic pain in nearly 30% of patients with idiopathic small fiber neuropathy, according to a genetic and electrophysiological study of patients with the mutations.

Other gain-of-function mutations in

the *SCN9A* gene that encodes  $Na_v1.7$  have been known to cause inherited erythromelalgia and paroxysmal extreme pain disorder, but this is the first time that such mutations have been reported in patients with biopsy-proven idiopathic small fiber neuropathy (I-SFN), reported Dr. Catharina G. Faber of University Medical Centre Maastricht (Netherlands) and her colleagues (*Ann. Neurol.* 2011 May 20 [doi:10.1002/ana.22485]).

The researchers advised that *SCN9A* gene analysis might be considered for patients with small fiber neuropathy in whom other causes are excluded, particularly patients with younger ages of onset.

During 2006-2009, Dr. Faber and her coauthors assessed 248 patients who were 18 years and older with a suspected clinical diagnosis of SFN. A total of 185 patients had an underlying cause of SFN, and 19 were lost to follow-up or refused

to participate. Inclusion and exclusion criteria were met by the remaining 44 patients. These patients had no identifiable underlying cause of SFN and had normal strength, tendon reflexes, vibration sense, and nerve conduction studies. They also had at least two neuropathic or autonomic symptoms.

Following skin biopsy and quantitative sensory testing (QST), 28 patients met cri-

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## Phenylketonurics

VIMPAT oral solution contains aspartame, a source of phenylalanine. A 200 mg dose of VIMPAT oral solution (equivalent to 20 mL) contains 0.32 mg of phenylalanine.

## ADVERSE REACTIONS

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 all controlled and uncontrolled trials in patients with partial-onset seizures, 1327 patients have received VIMPAT of whom 1000 have been treated for longer than 6 months and 852 for longer than 12 months.

## Clinical Trials Experience

### Controlled Trials

#### Adverse reactions leading to discontinuation

In controlled clinical trials, the rate of discontinuation as a result of an adverse event was 8% and 17% in patients randomized to receive VIMPAT 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 events most commonly (>1% in the VIMPAT total group and greater than placebo) leading to discontinuation were dizziness, ataxia, vomiting, diplopia, nausea, vertigo, and vision blurred.

#### Most common adverse reactions

Table 2 gives the incidence of treatment-emergent adverse events that occurred in  $\geq 2\%$  of adult patients with partial-onset seizures in the total VIMPAT group and for which the incidence was greater than placebo. The majority of adverse events in the VIMPAT patients were reported with a maximum intensity of 'mild' or 'moderate'.

**Table 2: Treatment-Emergent Adverse Event Incidence in Double-Blind, Placebo-Controlled Partial-Onset Seizure Trials (Events  $\geq 2\%$  of Patients in VIMPAT Total and More Frequent Than in the Placebo Group)**

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

## Laboratory abnormalities

Abnormalities in liver function tests have been observed in controlled trials with VIMPAT in adult patients with partial-onset seizures who were taking 1 to 3 concomitant anti-epileptic drugs. Elevations of ALT to  $\geq 3 \times$  ULN occurred in 0.7% (7/935) of VIMPAT patients and 0% (0/356) of placebo patients. One case of hepatitis with transaminases  $>20 \times$  ULN was observed in one healthy subject 10 days after VIMPAT 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 VIMPAT.

## Other Adverse Reactions in Patients with Partial-Onset Seizures

The following is a list of treatment-emergent adverse events reported by patients treated with VIMPAT in all clinical trials in patients with partial-onset seizures, including controlled trials and long-term open-label extension trials. Events addressed in other tables or sections are not listed here. Events included in this list from the controlled trials occurred more frequently on drug than on placebo and were based on consideration of VIMPAT pharmacology, frequency above that expected in the population, seriousness, and likelihood of a relationship to VIMPAT. Events are further classified within system organ class.

*Blood and lymphatic system disorders:* neutropenia, anemia

*Cardiac disorders:* palpitations

*Ear and labyrinth disorders:* tinnitus

*Gastrointestinal disorders:* constipation, dyspepsia, dry mouth, oral hypoesthesia

*General disorders and administration site conditions:* irritability, pyrexia, feeling drunk

*Injury, poisoning, and procedural complications:* fall

*Musculoskeletal and connective tissue disorders:* muscle spasms

*Nervous system disorders:* paresthesia, cognitive disorder, hypoesthesia, dysarthria, disturbance in attention, cerebellar syndrome

*Psychiatric disorders:* confusional state, mood altered, depressed mood

## Intravenous Adverse Reactions

Adverse reactions with intravenous administration generally appeared similar to those observed with the oral formulation, although intravenous administration was associated with local adverse events such as injection site pain or discomfort (2.5%), irritation (1%), and erythema (0.5%). One case of profound bradycardia (26 bpm; BP 100/60 mmHg) was observed in a patient during a 15 minute infusion of 150mg VIMPAT. This patient was on a beta-blocker. Infusion was discontinued and the patient experienced a rapid recovery.

## Comparison of Gender and Race

The overall adverse event 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.

## Postmarketing Experience

The following adverse reactions have been identified during postapproval use of VIMPAT. 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.

*Cardiac disorders:* Bradycardia

*Skin and subcutaneous tissue disorders:* Rash

## DRUG INTERACTIONS

Drug-drug interaction studies in healthy subjects showed no pharmacokinetic interactions between VIMPAT and carbamazepine, valproate, digoxin, metformin, omeprazole, or an oral contraceptive containing ethinylestradiol and levonorgestrel. There was no evidence for any relevant drug-drug interaction of VIMPAT with common AEDs in the placebo-controlled clinical trials in patients with partial-onset seizures [see *Clinical Pharmacology (12.3)* in Full Prescribing Information].

The lack of pharmacokinetic interaction does not rule out the possibility of pharmacodynamic interactions, particularly among drugs that affect the heart conduction system.

## USE IN SPECIFIC POPULATIONS

### 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.

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teria for I-SFN, which included reduced intraepidermal nerve fiber density and abnormal QST. All 28 patients were white.

Overall, 8 (29%) of the 28 patients with I-SFN had a missense mutation in the SCN9A gene. All patients were heterozygous for the mutation. No mutations were detected in SCN9A in 100 healthy control patients. Patients with SCN9A mutations were younger, albeit not significantly, than were the 20 patients without mutations (32.4 years vs. 42.7 years). No other clinical character-

istics differed between the two groups.

All but two of the eight reported that their pain, which varied in intensity and quality from patient to patient, began in their distal extremities. Seven of the patients with mutations described autonomic problems.

Electrophysiological analyses of cultured dorsal root ganglion neurons that were transfected with the mutated sodium channels indicated that the mutations changed the function of the channel such that they conferred a hyperexcitable state to the neurons.

Dr. Faber and her associates wrote

that the mutations in Na<sub>v</sub>1.7 may trigger axonal degeneration because “sodium influx is known to impose an energetic load on neurons and neuronal processes, and increased activity of mutant Na<sub>v</sub>1.7 channels would be expected to have an especially large effect on small-diameter intracutaneous axons.”

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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)] ≈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<sub>max</sub> 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<sub>CR</sub>≤30mL/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.

## A Little Less Idiopathic

**S**mall fiber polyneuropathy (SFPN) is one of those common diseases that many have never heard of. Neurologists focus on diseases of myelinated axons, but most axons are unmyelinated and thinly myelinated “small fibers.” These tiny axons are invisible to light microscopy and conventional electro-physiology; thus, small fiber diseases remain largely unexplored. In addition, their cardinal symptom is chronic pain, a condition often avoided like a modern plague.

Two recent objective tests, neurodiagnostic skin biopsy and autonomic function testing, now facilitate the diagnosis of small fiber diseases (Neurology 2009;72:177-84) but do not identify their cause. Most SFPN is labeled “idiopathic,” which translates from Latin as “we are idiots” and translates for our patients as “no possibility of cure.” This study reports that a substantial minority of Dutch SFPN patients have gain-of-function mutations in a sodium channel enriched in small fibers. It will be important to replicate these findings because they come from a carefully selected subset of patients.

These findings remind us that a substantial portion of unexplained chronic pain is neurological, and that neurologists need to engage with such patients. If such mutations are common, testing may develop, along with family-planning questions. The patients will increasingly seek testing and treatment for SFPN, but few neurology groups are currently equipped to do this. Fortunately, any physician can perform skin biopsy and mail the punches to academic or commercial laboratories for analysis. Sodium channel blockers will be used more for treating SFPN and other neuropathic pain. Neurologists will need to learn to prescribe mexiletine and continuous subcutaneous lidocaine along with carbamazepine (Neurology 2004;62:218-25).

ANNE LOUISE OAKLANDER, M.D., directs Massachusetts General Hospital's neurodiagnostic skin biopsy laboratory. She investigates neurological causes of chronic pain and wrote her commentary upon request. She has no disclosures.

VIEW ON THE NEWS



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