Major Finding: Men with spinal and bulbar muscular atrophy (SBMA) treated with dutasteride 2 years had significantly better physical quality of life, but significantly worse mental quality of life, than did placebo-treated patients. No differences in muscle strength were found.

Data Source: A phase II, randomized, double-blind, placebo-controlled trial of 50 men.

Disclosures: The trial was funded by the National Institute of Neurological Diseases and Stroke. None of the investigators had relevant disclosures.

VIMPAT® (lacosamide) Tablets, CV
VIMPAT® (lacosamide) Injection, CV
Brief Summary of Full Prescribing Information (See Package Insert for Full Prescribing Information)

Rx Only

INDICATIONS AND USAGE
Partial-Onset Seizures
VIMPAT (lacosamide) tablets are indicated as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older. VIMPAT (lacosamide) injection for intravenous use is indicated as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older when oral administration is not feasible.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Suicidal Behavior and Ideation
Anti-epileptic drugs (AEDs), including VIMPAT, increase the risk of suicidal thoughts or behavior and lethargy 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 19 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had a risk for suicidal behavior or ideation seven times higher than 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 16,029 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 with AEDs 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 of 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 (≥6-100 years) in the clinical trials analyzed.

Table 1 Risk by indication for anti-epileptic drugs in the pooled analysis

<table>
<thead>
<tr>
<th>Indication</th>
<th>Placebo Patients with Events Per 1000 Patients</th>
<th>Drug Patients with Events Per 1000 Patients</th>
<th>Relative Risk of Incidence in Placebo Patients</th>
<th>Risk Difference: Additional Drug Patients with Events Per 1000 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>1.0</td>
<td>3.4</td>
<td>3.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>5.7</td>
<td>8.5</td>
<td>1.5</td>
<td>2.9</td>
</tr>
<tr>
<td>Other</td>
<td>1.0</td>
<td>1.6</td>
<td>1.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Total</td>
<td>2.4</td>
<td>4.3</td>
<td>1.8</td>
<td>1.9</td>
</tr>
</tbody>
</table>

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

Anyone considering prescribing VIMPAT or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which anti-epileptics are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and 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. Behavior of concern should be reported immediately to healthcare providers.

Dizziness and Ataxia
Patients should be advised that VIMPAT may cause dizziness and ataxia. Accordingly, they should be advised not to drive a car or to operate other complex machinery until they are familiar with the effects of VIMPAT on their ability to perform such activities.

In patients with partial-onset seizures taking 1 to 3 concomitant AEDs, dizziness was experienced by 20% of patients randomized to the recommended doses (200 to 400 mg/day) of VIMPAT (compared with 8% of placebo patients) and was the adverse event most frequently leading to discontinuation. Ataxia was experienced by 6% of patients randomized to the recommended doses (200 to 400 mg/day) of VIMPAT (compared with 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/Table 2 [6.1])

Carotid Rhythm and Conduction Abnormalities
PR interval prolongation
Dose-dependent prolongations in PR interval with VIMPAT have been observed in clinical studies in patients and in healthy volunteers (see Clinical Pharmacology [12.2] in Full Prescribing Information). In clinical trials in patients with partial-onset epilepsy, asymptomatic first-degree atrioventricular (AV) block was observed as an adverse reaction in 0.4% (4/940) of patients randomized to receive VIMPAT and 0% (0/364) of patients randomized to placebo. In clinical trials in patients with diabetic neuroarayopathy, asymptomatic first-degree AV block was observed as an adverse reaction in 0.5% (5/1023) of patients receiving VIMPAT and 0% (0/291) of patients receiving placebo. When VIMPAT is given with other drugs that prolong the PR interval, further PR prolongation is possible.

VIMPAT 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), or with severe cardiac disease such as myocardial ischemia or heart failure. In such patients, obtaining an ECG before beginning VIMPAT, and after VIMPAT is titrated to steady-state, is recommended.

Atrial fibrillation and Atrial flutter
In the short-term investigational trials of VIMPAT in epilepsy patients, there were no cases of atrial fibrillation or flutter. In patients with diabetic neuropathy, 0.5% of patients treated with VIMPAT experienced an adverse reaction of atrial fibrillation or flutter, compared to 0% of placebo-treated patients. The administration of VIMPAT may predispose to atrial arrhythmias (atrial fibrillation or flutter), especially in patients with diabetic neuropathy and/or cardiovascular disease. Patients should be made aware of the symptoms of atrial fibrillation and flutter (e.g., palpitations, rapid pulse, shortness of breath) and told to contact their physician should any of these symptoms occur.

Syncope
In the short-term controlled trials of VIMPAT in epilepsy patients with no significant system illnesses, there was no increase in syncope compared to placebo. In the short-term controlled trials of VIMPAT in patients with diabetic neuropathy, 1.2% of patients who were treated with VIMPAT 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 tachycardia.

Withdrawal of Anti-epileptic Drugs (AEDs)
As with all AEDs, VIMPAT should be withdrawn gradually (over a minimum of 1 week) to minimize the potential of increased seizure frequency in patients with seizure disorders.

Multifactor Hypersensitivities Reactions
One case of symptomatic hypocalcemia and nephritis was observed among 4011 subjects exposed to VIMPAT during clinical development. The event occurred in a healthy volunteer, 10 days after stopping VIMPAT 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 multifactor hypersensitivity reaction. Additional potential cases included 2 with rash and elevated liver enzymes and 1 with myocarditis and hepatitis of uncertain etiology.

Multifactor hypersensitivity reactions (also known as Drug Reaction with Eosinophilia and Systemic Symptoms, or DRESS) have been reported with other anti-epileptics 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 pericarditis. Because the myocarditis is variable in its expression, other organ system signs and symptoms not noted here may occur. If this reaction is suspected, VIMPAT should be discontinued and alternative treatment started.

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.
been thought to be a potential therapy for SBMA because experiments in mice that were bred to express the mutant androgen receptor showed that reducing androgen levels could mitigate the toxicity of the mutant phenotype.

To evaluate the efficacy and safety of dutasteride (Avodart), Dr. Kenneth H. Fischbeck, chief of the Neurogenetics Branch of the National Institute of Neurological Diseases and Stroke and his colleagues randomized 50 men with SBMA to either 0.5 mg/day of dutasteride or placebo. That dose of dutasteride is the same as that approved for treating symptomatic benign prostatic hyperplasia.

The men in each group were an average age of about 53 years, and had an average CAG repeat length of 4 codons (compared with wild-type human repeat length of 36 codons or less), a mean duration of weakness of about 12 years, and an average body mass index of about 28 kg/m². After 2 years, patients treated with dutasteride had virtually no appreciable increase in weight-scaled quantitative muscle assessment scores from baseline—the primary efficacy measure—whereas the scores in patients taking placebo declined by 5% from baseline. This difference was not significant, according to the investigators, who reported their results in a plenary session at the annual meeting of the American Neurological Association.

On the Short Form–36 quality of life questionnaire (version 2), the physical component summary improved by about 14% from baseline for dutasteride-treated patients, which was significantly different from the 10% drop recorded in placebo-treated patients. Significantly fewer falls occurred among patients who were treated with dutasteride than among those who received placebo (9 patients reporting 40 falls vs. 16 subjects reporting 63 falls). However, patients who took dutasteride fared more poorly than those who took placebo on the mental component summary of the questionnaire, in which patients on placebo had a 10% improvement and patients on dutasteride worsened by about 7%.

Modified barium swallow scores, a measurement for dysphagia severity, worsened by a similar amount in subsets of patients from both arms.

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, 26% 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, astasia, vomiting, diplopia, nausea, vertigo, and vision blurred.

#### Most common adverse reactions

Table 2 presents the incidence of treatment-emergent adverse events that occurred in ≥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 ≥2% of Patients in VIMPAT Total and More Frequent Than in the Placebo Group)

<table>
<thead>
<tr>
<th>System Organ Class/Preferred Term</th>
<th>Placebo N=364</th>
<th>VIMPAT 200 mg/day N=270</th>
<th>VIMPAT 400 mg/day N=471</th>
<th>VIMPAT 600 mg/day N=203</th>
<th>VIMPAT 100% N=844</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ear and labyrinth disorder</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertigo</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diplopia</td>
<td>2</td>
<td>6</td>
<td>10</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>3</td>
<td>2</td>
<td>9</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>4</td>
<td>7</td>
<td>11</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>6</td>
<td>9</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>6</td>
<td>7</td>
<td>7</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>2</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td><strong>Injury, poisoning and procedural complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contusion</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Skin laceration</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>8</td>
<td>16</td>
<td>36</td>
<td>53</td>
<td>31</td>
</tr>
<tr>
<td>Headache</td>
<td>11</td>
<td>14</td>
<td>12</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Ataxia</td>
<td>2</td>
<td>4</td>
<td>7</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Somnolence</td>
<td>5</td>
<td>5</td>
<td>8</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Tremor</td>
<td>4</td>
<td>4</td>
<td>6</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>2</td>
<td>4</td>
<td>5</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Balance disorder</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Skin and subcutaneous disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

**Laboratory abnormalities**

Abnormalities in liver function tests have been observed in controlled trials with VIMPAT in adult patients with seizures who were taking 1 to 3 concomitant anti-epileptic drugs. Elevations of ALT to ≥3× ULN occurred in 0.7% (7/935) of VIMPAT patients and 0% (0/356) of placebo patients. One case of hepatitis with transaminases ≥20× 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.

### Table: 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:**
- anemia
- neoplasms
- lymphoma

**Cardiac disorders:**
- palpitations
- tachycardia

**Ear and labyrinth disorders:**
- tinnitus
- vertigo
- deafness

**Gastrointestinal disorders:**
- constipation
- diarrhea
- abdominal pain

**General disorders and administration site conditions:**
- astasia
- vertigo
- blurred vision
- vomiting
- dyspepsia

**Hepatic and biliary disorders:**
- jaundice
- elevated liver enzymes

**Injury, poisoning and procedural complications:**
- fractures
- pain

**Mucocutaneous and connective tissue disorders:**
- muscle spasms
- alopecia

**Nervous system disorders:**
- dizziness
- headache
- tremor
- ataxia
- anxiety
- depression
- insomnia

**Ocular disorders:**
- diplopia
- strabismus

**Otorhinolaryngological disorders:**
- vertigo
- tinnitus

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

There were few non-Caucasian patients, no differences in the incidences of adverse events compared to Caucasian patients were observed.

**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%), flushing (1%), and hypertension (0.5%). One case of profound bradycardia (26 bpm; BP 109/60 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.

### Drug Interactions

Drug-drug interaction studies in healthy subjects showed no pharmacokinetic interactions between VIMPAT and carbamazepine, valproate, diazepam, mefloquine, ondansetron, or an oral contraceptive containing ethinyl estradiol 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. 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 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