PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrVIMPAT®

lacosamide tablets

Tablets, 50 mg, 100 mg, 150 mg, 200 mg, Oral

lacosamide injection

Solution for injection, 10 mg / mL, Intravenous

Antiepileptic

ATC Code: N03AX18

UCB Canada Inc.
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RECENT MAJOR LABEL CHANGES

7 Warnings and Precautions, 7.1.1 Pregnant Women	09/2022
7 Warnings and Precautions, 7.1.2 Breast-feeding	09/2022

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

VIMPAT (lacosamide) is indicated as:

- Monotherapy in the management of partial-onset seizures **in adult (≥18 years of age)** patients with epilepsy. All patients who participated in the monotherapy trial were newly or recently diagnosed with epilepsy (see 14 CLINICAL TRIALS).
- Adjunctive therapy in the management of partial-onset seizures in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy.

1.1 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of VIMPAT in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use (see 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics (≥65 years of age): The clinical experience with VIMPAT in elderly patients with epilepsy is limited. Caution should be exercised during dose titration and age-associated decreased renal clearance should be considered in elderly patients (see 7.1.4 Geriatrics, 4.2 Recommended Dose and Dosage Adjustment, Geriatrics and 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics).

2 CONTRAINDICATIONS

- Patients who are hypersensitive to VIMPAT or to any of the excipients. For a complete listing, see the 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section of the product monograph.
- Patients with a history of, or presence of, second- or third-degree atrioventricular (AV) block.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

VIMPAT may be taken with or without food.

Initiation

- VIMPAT therapy can be initiated with either oral or intravenous (IV) administration.
- VIMPAT solution for injection for IV use is an alternative when oral administration is temporarily not feasible.
- Conversion to or from oral and IV administration can be done directly without titration. The total daily dose and twice daily administration should be maintained.

4.2 Recommended Dose and Dosage Adjustment

Monotherapy

The recommended starting dose is 100 mg twice a day (200 mg/day), with or without food. Depending on patient response and tolerability, the dose can be further increased at weekly intervals by 50 mg twice a day (100 mg/day), to a maximum recommended maintenance daily dose of 300 mg twice a day (600 mg/day). In the monotherapy trial, the majority of patients who completed the Evaluation Phase of the study and remained seizure free received VIMPAT 200 or 400 mg/day (see 14.2 Study Results, Monotherapy).

In patients having reached VIMPAT ≥400mg/day and who need an additional antiepileptic drug, the dosing that is recommended for adjunctive therapy below should be followed. Maximum recommended daily dose for adjunctive therapy is 400 mg/day.

Adjunctive Therapy

The recommended starting dose for VIMPAT is 50 mg twice a day, with or without food, which should be increased to an initial therapeutic dose of 100 mg twice a day after one week. Depending on patient response and tolerability, the maintenance dose can be further increased by 50 mg twice a day every week, to a maximum recommended daily dose of 400 mg (200 mg twice a day). Doses above 400 mg/day do not confer additional benefit, are associated with more severe and substantially higher frequency of adverse reactions and are not recommended (see 5 OVERDOSAGE, Non-acute Overdose in Humans).

Patients with Renal Impairment

No dose adjustment is necessary in patients with mild or moderate renal impairment (creatinine clearance (CL_{CR}) >30 mL/min). A maximum dose of 300 mg/day is recommended for patients with severe renal impairment (CL_{CR} ≤30 mL/min) and in patients with end-stage renal disease. In all patients with any degree of renal impairment, the dose titration should be performed with caution (see 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency).

Following a 4-hour hemodialysis treatment, AUC of VIMPAT was reduced by approximately 50%. Thus, dosage supplementation of up to 50% following hemodialysis may be considered. Treatment of patients with end-stage renal disease should be made with caution as there is

limited clinical experience in subjects (n=8) and no experience in patients, and there is accumulation of a metabolite (with no known pharmacological activity).

Patients with Hepatic Impairment

The dose titration should be performed with caution in patients with mild to moderate hepatic impairment. A maximum dose of 300 mg/day is recommended for patients with mild or moderate hepatic impairment. The pharmacokinetics of VIMPAT have not been evaluated in severe hepatic impairment. VIMPAT is not recommended in patients with severe hepatic impairment (see 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency).

Pediatrics (<18 years of age)

The safety and effectiveness of VIMPAT in pediatric patients <18 years has not been established, and therefore its use in this patient population is not indicated (see 1.1 Pediatrics and 7.1.3 Pediatrics).

Geriatrics (≥ 65 years of age)

Clinical experience with VIMPAT in elderly patients with epilepsy is limited. Although no dose reduction is necessary in elderly patients, caution should be exercised during dose titration and age-associated decreased renal clearance with an increase in AUC levels should be considered in elderly patients (see 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics).

Discontinuation

In accordance with current clinical practice, if VIMPAT has to be discontinued, it is recommended this be done gradually (e.g. taper the daily dose by 200 mg/week).

4.3 Reconstitution

Solution for injection

VIMPAT solution for injection can be administered intravenously without further dilution or may be mixed with diluents. VIMPAT solution for injection was found to be physically compatible and chemically stable when mixed with the following diluents for at least 24 hours and stored in glass or polyvinyl chloride (PVC) bags at room temperature 15-30°C.

Diluents

- Sodium Chloride Injection 0.9% (w/v)
- Dextrose Injection 5% (w/v)
- Lactated Ringer's Injection

The stability of VIMPAT solution for injection in other infusion solutions has not been evaluated. Product with particulate matter or discoloration should not be used.

4.4 Administration

Film-coated tablets

The film-coated tablets are taken orally twice a day. The tablet must not be divided or crushed. For further directions for use, see 4.2 Recommended Dose and Dosage Adjustment section of the product monograph.

Solution for injection

The solution for injection is infused over a period of 30 to 60 minutes twice daily. VIMPAT solution for injection can be administered intravenously without further dilution. There is experience with twice daily infusions of VIMPAT up to 5 days (n=53).

Do not use if product shows haziness, particulate matter, discoloration or leakage. Any unused portion of VIMPAT solution for injection should be discarded. See 11 STORAGE, STABILITY AND DISPOSAL**.**

4.5 Missed Dose

If the patient misses a dose by a few hours, they should be instructed to take VIMPAT as soon as they remember. If it is close to their next dose, they should be instructed to take their medication at the next regular time. Patients should not take two doses at the same time.

5 OVERDOSAGE

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

Lowest known lethal dose: estimated 7g (age 56, male) (see below).

The types of adverse events experienced by patients exposed to acute VIMPAT overdose during pre-marketing clinical trials were mostly similar to those observed in patients administered therapeutic doses of VIMPAT.

Following doses above 400 mg/day up to 800 mg/day, the more commonly reported adverse events were related to the central nervous system (dizziness, headache, fatigue) and the gastrointestinal system (nausea and vomiting).

There has been a single case of intentional overdose in a clinical trial by a patient who self-administered 12000 mg VIMPAT along with large doses of zonisamide, topiramate, and gabapentin. The patient was initially comatose, had second degree AV block, seizures, and was hospitalized. An EEG revealed epileptic waveforms. The patient recovered 2 days later. From

the 9 cases in pre-marketing clinical studies exposed to an acute VIMPAT overdose >800 mg, none resulted in death.

Decreased visual acuity was reported in one case from a clinical trial of VIMPAT overdose at 1050 mg within a single day. The event was considered non-serious and resolved the following day.

In post-marketing experience, events reported following acute single overdoses ranging between 800 mg and 12000 mg were dizziness, nausea, vision abnormalities, seizures (generalized tonic-clonic seizures, status epilepticus), cardiac conduction disorders, shock and coma. Fatal cardiac arrest, shock and multi-organ failure were reported following acute overdoses of 7000 mg of VIMPAT.

There have also been post-marketing reports of seizures and loss of consciousness in patients with acute single VIMPAT overdoses between 400 mg and 1200 mg.

Non-acute Overdose in Humans

Non-acute VIMPAT overdose has also been reported. The great majority of these cases were in patients receiving daily VIMPAT doses ≤ 800 mg for various durations. Adverse events observed after supratherapeutic doses included vision abnormalities (blurred vision, diplopia, nystagmus), cardiac arrhythmia, status epilepticus, convulsions and increased seizure frequency and duration. For example, in one case, after receiving VIMPAT 900 mg/day for 23 days, a patient experienced increased seizure duration and frequency. The maximum recommended daily dose of VIMPAT as adjunctive and monotherapy in patients with partial onset seizures is 400 mg and 600 mg, respectively. Higher doses are not recommended (see 4.2 Recommended Dose and Dosage Adjustment).

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 Poison Control Centre 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 helpful based on the patient's clinical state or in patients with significant renal impairment.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	film-coated tablets / 50 mg, 100 mg, 150 mg, 200 mg / bottles and blisters	colloidal silicon dioxide, crospovidone, hydroxypropylcellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide and dye pigments as specified below. VIMPAT film-coated tablets are supplied as debossed tablets and contain the following coloring agents: 50 mg tablets: black iron oxide, FD&C Blue #2/indigo carmine aluminum lake, red iron oxide 100 mg tablets: yellow iron oxide 150 mg tablets: black iron oxide, red iron oxide, yellow iron oxide 200 mg tablets: FD&C Blue #2/indigo carmine aluminum lake
intravenous	solution for injection / 10 mg/mL / vial	hydrochloric acid, sodium chloride, water for injection

VIMPAT film-coated tablets

VIMPAT film-coated tablets are supplied as follows:

50 mg tablet: VIMPAT tablets 50 mg lacosamide are pink, oval, film-coated tablets debossed with "SP" on one side and "50" on the other. They are supplied in high density polyethylene (HDPE) bottles of 60, 180, 500, and 1000, and as blisters (with polyvinyl chloride (PVC) and polyvinylidene chloride (PVDC) bottom film and aluminum top foil) of 14 tablets.

100 mg tablet: VIMPAT tablets 100 mg lacosamide are dark yellow, oval, film-coated tablets debossed with "SP" on one side and "100" on the other. They are supplied in HDPE bottles of 60, 180, 500, and 1000 and as blisters (with PVC and PVDC bottom film and aluminum top foil) of 14 tablets.

150 mg tablet: VIMPAT tablets 150 mg lacosamide are salmon, oval, film-coated tablets debossed with "SP" on one side and "150" on the other. They are supplied in HDPE bottles of 60, 180, 500, and 1000.

200 mg tablet: VIMPAT tablets 200 mg lacosamide are blue, oval, film-coated tablets debossed with "SP" on one side and "200" on the other. They are supplied in HDPE bottles of 60, 180, 500, and 1000.

In addition, a 2 week titration pack containing separate blisters of 50 mg and 100 mg tablets is available. There are 14 tablets of each strength per blister.

VIMPAT solution for injection

VIMPAT solution for injection is a clear, colorless, sterile solution containing 20 mL of 10 mg lacosamide per mL for intravenous infusion. Hydrochloric acid is used for pH adjustment. VIMPAT solution for injection has a pH of 3.8 to 5.0.

VIMPAT solution for injection 10 mg/mL is supplied in 20 mL colorless single-use glass vials, 10 mg/mL vial.

7 WARNINGS AND PRECAUTIONS

General

Withdrawal of Antiepileptic 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 (see 4.2 Recommended Dose and Dosage Adjustment, Discontinuation).

Carcinogenesis and Mutagenesis

See 16 NON-CLINICAL TOXICOLOGY, Carcinogenesis and Mutagenesis for discussion on animal data.

Cardiovascular

Cardiac Rhythm and Conduction Abnormalities

- **PR Interval Prolongation**

In post-marketing experience, atrioventricular (AV) block (including second degree or higher AV block) has been reported. In patients with proarrhythmic conditions, ventricular tachyarrhythmia has been rarely reported. In rare cases, these events have led to asystole, cardiac arrest and death in patients with underlying proarrhythmic conditions.

Patients should be made aware of the symptoms of cardiac arrhythmia (e.g. slow, rapid, or irregular pulse, palpitations, shortness of breath, feeling lightheaded, fainting), and told to seek immediate medical advice if these symptoms occur.

In patients who develop serious cardiac arrhythmia, VIMPAT should be discontinued and a thorough clinical benefit/risk assessment should be performed before possibly restarting therapy.

VIMPAT should be used with caution in patients with underlying proarrhythmic conditions such as patients with known cardiac conduction problems (e.g. marked first-degree AV block, sick sinus syndrome without pacemaker), or severe cardiac disease (e.g. myocardial ischemia/infarction, heart failure, structural heart disease, or cardiac sodium channelopathies) or patients treated with medicinal products affecting cardiac conduction (see 9.2 Drug Interactions Overview). In such patients, obtaining an ECG before beginning VIMPAT, and after VIMPAT is titrated to steady-state, is recommended.

Caution should especially be exerted when treating elderly patients as they may be at increased risk of cardiac disorder or when VIMPAT is given with other drugs that prolong the PR interval (e.g. sodium channel blocking antiepileptic drugs, pregabalin, or beta-blockers), as further PR prolongation is possible (see 8.2 Clinical Trial Adverse Reactions, Cardiac and 9.2 Drug Interactions Overview). In these patients it should be considered to perform an ECG before a VIMPAT dose increase above 400mg/day and after VIMPAT is titrated to steady-state.

In clinical trials of healthy subjects and patients with epilepsy, VIMPAT treatment was associated with PR interval prolongation in a dose-dependent manner (see 10.2 Pharmacodynamics, Cardiac Electrophysiology). Patients with significant electrocardiographic (ECG) abnormalities were systematically excluded from these trials. The mean PR interval increase (at t_{max}) in a clinical pharmacology ECG trial of healthy subjects was 13.6ms for the 400mg/day VIMPAT group, 18.2ms for the 800mg/day VIMPAT group, and 6.3ms for the placebo group. The mean increase in PR interval at the end of 12 weeks maintenance treatment for patients with partial-onset seizures who participated in the controlled adjunctive therapy trials was 1.4ms, 4.4ms, and 6.6ms for the VIMPAT 200, 400, and 600mg/day groups, respectively, and -0.3ms for the placebo group. The mean maximum increase in PR interval in these controlled trials was 12.7ms, 14.3ms, and 15.7ms in the VIMPAT 200, 400, and 600mg/day groups and 11.2ms in the placebo group. Among patients who participated in these controlled trials, asymptomatic first-degree atrioventricular (AV) block was detected on ECG and reported as an adverse reaction for 0.4% (4/944 patients) in the VIMPAT group and 0% (0/364 patients) in the placebo group (see 8.2 Clinical Trial Adverse Reactions, Cardiac).

- **Atrial Fibrillation and Atrial Flutter**

VIMPAT administration 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 or irregular pulse, shortness of breath) and told to contact their physician should any of these symptoms occur.

Atrial fibrillation and flutter have been reported in open-label epilepsy trials and in post-marketing experience. No cases occurred in the short-term investigational trials of VIMPAT in epilepsy patients. In patients with diabetic neuropathy, 0.6% of patients treated with VIMPAT experienced an adverse reaction of atrial fibrillation or atrial flutter, compared to 0% of placebo-treated patients.

Driving and Operating Machinery

Patients should be advised not to drive a car or to operate other complex machinery or perform hazardous tasks until they are familiar with the effects of VIMPAT on their ability to perform such activities (see 7 WARNINGS AND PRECAUTIONS, Neurologic).

Hepatic/Biliary/Pancreatic

Rare post-marketing reports of severe liver injury, including acute liver failure, have been reported in patients treated with VIMPAT. Some of the cases were considered clinically significant and possibly or probably related to VIMPAT therapy. Laboratory testing to determine liver enzyme levels should be done upon the first symptom or sign of liver dysfunction (e.g., pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained "flu-like" symptoms). VIMPAT should be discontinued in patients with jaundice or laboratory evidence of liver injury and alternative therapy should be considered (see 8.5 Post-Market Adverse Drug Reactions, Hepatic/Biliary/Pancreatic).

Immune

Hypersensitivity

Multiorgan hypersensitivity reactions (including Drug Reaction with Eosinophilia and Systemic Symptoms, or DRESS), Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported with anticonvulsants, including VIMPAT.

Typically, although not exclusively, DRESS presents with fever and rash associated with other organ system involvement, that may or may not include eosinophilia, hepatitis, nephritis, lymphadenopathy, and/or myocarditis. Because these disorders are variable in their expression, other organ system signs and symptoms not noted here may also occur. If any of these hypersensitivity reactions are suspected, VIMPAT should be discontinued and alternative treatment started.

One case of symptomatic hepatitis 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 multiorgan hypersensitivity reaction. Additional potential cases included 2 with rash and elevated liver enzymes and 1 with myocarditis and hepatitis of uncertain etiology.

SJS has been reported very rarely in post-marketing experience during treatment with VIMPAT in combination with other antiepileptic drugs. A causal relationship between SJS and VIMPAT treatment cannot be excluded. SJS was not reported during clinical development.

No cases of TEN were reported during clinical development. TEN has been reported very rarely in post-marketing experience during treatment with VIMPAT in combination with other drugs including antiepileptic drugs. A causal relationship between TEN and VIMPAT treatment cannot be excluded.

Monitoring and Laboratory Tests

See 7 WARNINGS AND PRECAUTIONS, Cardiovascular.

Neurologic

Dizziness and Ataxia

Treatment with VIMPAT has been associated with dizziness and ataxia which could increase the occurrence of accidental injury or falls (see 7 WARNINGS AND PRECAUTIONS, Driving and Operating Machinery).

In controlled adjunctive therapy clinical trials, dizziness was experienced by 25% of patients with partial-onset seizures taking 1 to 3 concomitant AEDs 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 (3%). Ataxia was experienced by 6% of patients randomized to the recommended doses (200 to 400 mg/day) of VIMPAT (compared to 2% of placebo patients) (see 8.2 Clinical Trial Adverse Drug Reactions). There was a substantial increase in the frequency of occurrence of these events when patients received VIMPAT doses greater than 400 mg/day.

Ophthalmologic

In controlled adjunctive therapy trials in patients with partial-onset seizures, VIMPAT treatment was associated with vision-related adverse events such as blurred vision (VIMPAT, 8%; placebo, 3%) and diplopia (VIMPAT, 11%; placebo, 2%). Three percent of patients randomized to VIMPAT discontinued treatment due to vision-related adverse events (primarily diplopia) (see 8 ADVERSE REACTIONS).

Patients should be informed that if visual disturbances occur, they should notify their physician promptly. If visual disturbance persists, further assessment, including dose reduction and possible discontinuation of VIMPAT, should be considered. More frequent assessments should

be considered for patients with known vision-related issues or those who are already routinely monitored for ocular conditions.

Psychiatric

Suicidal Ideation and Behaviour

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications.

All patients treated with antiepileptic drugs, irrespective of indication, should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

An FDA meta-analysis of randomized placebo controlled trials, in which antiepileptic drugs were used for various indications, has shown a small increased risk of suicidal ideation and behaviour in patients treated with these drugs. The mechanism of this risk is not known.

There were 43892 patients treated in the placebo controlled clinical trials that were included in the meta-analysis. Approximately 75% of patients in these clinical trials were treated for indications other than epilepsy and, for the majority of non-epilepsy indications the treatment (antiepileptic drug or placebo) was administered as monotherapy. Patients with epilepsy represented approximately 25% of the total number of patients treated in the placebo controlled clinical trials and, for the majority of epilepsy patients, treatment (antiepileptic drug or placebo) was administered as adjunct to other antiepileptic agents (i.e., patients in both treatment arms were being treated with one or more antiepileptic drug). Therefore, the small increased risk of suicidal ideation and behaviour reported from the meta-analysis (0.43% for patients on antiepileptic drugs compared to 0.24% for patients on placebo) is based largely on patients that received monotherapy treatment (antiepileptic drug or placebo) for non-epilepsy indications. The study design does not allow an estimation of the risk of suicidal ideation and behaviour for patients with epilepsy that are taking antiepileptic drugs, due both to this population being the minority in the study, and the drug-placebo comparison in this population being confounded by the presence of adjunct antiepileptic drug treatment in both arms.

Reproductive Health: Female and Male Potential

- **Women of Childbearing Potential / Contraception**

There was no clinically relevant interaction between lacosamide and oral contraceptives (ethinylestradiol and levonorgestrel) in clinical studies (see 9.4 Drug-Drug Interactions, Oral Contraceptives).

- **Fertility**

No adverse effects on male or female fertility or reproduction were observed in rats at doses producing plasma exposures (AUC) up to approximately 2 times the plasma AUC in humans at the maximum recommended human dose (MRHD) of 400 mg/day.

Syncope

In the short-term controlled adjunctive therapy 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, 1.0% 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 bradycardia. In the controlled monotherapy trial, seven patients (1.6%) reported syncope in the VIMPAT-treated group during the treatment period (see 8.2 Clinical Trial Adverse Reactions, Syncope).

7.1 Special Populations

7.1.1 Pregnant Women

There are no clinical studies with VIMPAT in pregnant women. Studies in pregnant rats revealed that lacosamide and/or its metabolites readily crossed the placental barrier. Data in rats and rabbits did not indicate teratogenic effects but embryotoxicity was observed at maternal toxic doses (see 5 OVERDOSAGE, Non-acute Overdose in Humans; 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

There are postmarketing reports of VIMPAT crossing the placental barrier in humans. Since the potential risk for humans is not established, VIMPAT should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus. If women decide to become pregnant while taking VIMPAT, the use of this product should be carefully re-evaluated.

Pregnancy Registry: Physicians are advised to recommend that pregnant patients taking VIMPAT enroll in the North American Antiepileptic Drug (NAAED) 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 following website: http://www.aedpregnancyregistry.org/

7.1.2 Breast-feeding

Lacosamide is excreted in human breast milk in significant quantities. Mother's milk/plasma ratios of 0.5 to 0.83 have been reported. A decision should be made whether to discontinue nursing or to discontinue lacosamide, taking into account the benefits of the drug to the mother and any potential adverse effects of lacosamide on the breastfed infant.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): VIMPAT is not indicated for use in pediatrics (< 18 years of age) as there is insufficient data on safety and efficacy of the drug in this population (see 1.1 Pediatrics and 4.2 Recommended Dose and Dose Adjustment, Pediatrics).

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): The experience with VIMPAT in elderly patients with epilepsy is limited. Although no dose reduction is necessary in elderly patients, caution should be exercised during dose titration and age-associated decreased renal clearance with an increase in AUC levels should be considered in elderly patients (see 4.2 Recommended Dose and Dose Adjustment, Geriatrics and 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In controlled adjunctive therapy clinical trials in patients with partial-onset seizures, 924 patients received VIMPAT. In the controlled monotherapy clinical trial in patients with partial-onset seizures, 444 patients received at least one dose of VIMPAT.

Some of the most frequently reported adverse reactions in controlled clinical trials with lacosamide treatment were dizziness, headache, nausea, and vision-related events (e.g. diplopia, blurred vision). They were dose-related and usually mild to moderate in intensity.

The adverse event profile for the monotherapy clinical trial was similar to that of the adjunctive therapy trials with some exceptions (see below).

In controlled adjunctive therapy clinical trials in patients with partial-onset seizures, the rate of discontinuation as a result of an adverse event was 8% and 17% in patients randomized to receive VIMPAT at doses of 200 and 400 mg/day, respectively (placebo: 5%). At VIMPAT doses of 600 mg/day, 29% of the patients discontinued the trials due to adverse events. The adverse events most commonly (≥1% in the VIMPAT total group and greater than placebo) leading to discontinuation were dizziness, coordination abnormal, vomiting, diplopia, nausea, vertigo, and vision blurred. Other adverse events that led to discontinuation (<1% in the VIMPAT total

group and greater than placebo) were typically central nervous system (CNS) related and included tremor, nystagmus, fatigue, balance disorder, and disturbance in attention.

In the controlled monotherapy clinical trial in patients with partial-onset seizures, the rate of discontinuation as a result of an adverse event was 10.6% for patients treated with VIMPAT and 15.6% for patients treated with active comparator [carbamazepine (controlled-release)]. The adverse event most commonly (≥1% in the VIMPAT treatment group) leading to discontinuation was dizziness (1.4%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adjunctive Therapy and Monotherapy

Table 2 gives the incidence of treatment-emergent adverse events that occurred in ≥1% of adult patients with partial-onset seizures in the total VIMPAT group (n=944) and for which the frequency was greater than placebo, in controlled adjunctive therapy clinical trials. The majority of adverse events were reported with a maximum intensity of 'mild' or 'moderate'.

Table 2 - Treatment-Emergent Adverse Event Incidence in Double-Blind, Placebo-Controlled Adjunctive Therapy Partial-Onset Seizure Trials (Events ≥1% of Patients in the total VIMPAT group and More Frequent Than in the Placebo Group)

MedDRA System Organ Class/ Preferred Term	Placebo N=364 %	200 g/day N=270 %	400 g/day N=471 %	600 g/day N=203 %
Ear and labyrinth disorders				
Vertigo	1	5	3	4
Tinnitus	1	0	2	2
Eye disorders				
Diplopia	2	6	10	16
Vision blurred	3	2	9	16
Conjunctivitis	<1	2	<1	0

MedDRA System Organ Class/ Preferred Term	Placebo N=364 %	200 g/day N=270 %	400 g/day N=471 %	600 g/day N=203 %
Gastrointestinal disorders				
Nausea	4	7	11	17
Vomiting	3	6	9	16
Diarrhoea	3	3	5	4
Constipation	1	1	2	4
Flatulence	0	3	2	1
Dyspepsia	1	1	2	2
Toothache	1	2	2	1
Dry Mouth	1	1	1	2
Hypoaesthesia oral	0	0	1	1
General disorders and administration site conditions				
Fatigue	6	7	7	15
Gait disturbance	<1	<1	2	4
Asthenia	1	2	2	4
Irritability	1	1	2	2
Chest pain	1	2	1	2
Pyrexia	1	2	1	1
Feeling drunk	0	0	1	3
Oedema peripheral	0	1	<1	2
Feeling abnormal	<1	0	1	2
Infections and infestations				
Nasopharyngitis	6	6	8	4
Bronchitis	0	2	1	1
Rhinitis	<1	<1	1	1
Ear infection	<1	1	1	0
Cystitis	<1	1	<1	1
Gastroenteritis	0	1	<1	0

MedDRA System Organ Class/ Preferred Term	Placebo N=364 %	200 g/day N=270 %	400 g/day N=471 %	600 g/day N=203 %
Injury, poisoning and procedural complications				
Contusion	3	3	4	2
Skin laceration	2	2	3	3
Fall	<1	1	2	1
Head injury	<1	2	1	1
Joint sprain	0	1	1	2
Investigations				
Positive rombergism	0	1	1	2
Gamma-glutamyltransferase increased	<1	2	<1	1
White blood cell count decreased	<1	0	<1	2
Metabolism and nutrition disorders				
Decreased appetite	<1	<1	2	3
Hypercholesterolaemia	<1	1	1	1
Musculoskeletal and connective tissue disorders				
Muscle spasms	<1	1	1	2
Neck pain	<1	1	1	1
Nervous system disorders				
Dizziness	8	16	30	53
Headache	9	11	14	12
Ataxia	2	4	7	15
Somnolence	5	5	8	8
Tremor	4	4	6	12
Nystagmus	4	2	5	10
Balance disorder	0	1	5	6
Memory Impairment	2	1	2	6
Cognitive disorder	<1	<1	2	2

MedDRA System Organ Class/ Preferred Term	Placebo N=364 %	200 g/day N=270 %	400 g/day N=471 %	600 g/day N=203 %
Hypoaesthesia	1	2	2	2
Dysarthria	<1	<1	1	3
Disturbance in attention	1	0	1	2
Psychiatric disorders				
Depression	1	2	2	2
Insomnia	1	2	2	1
Confusional state	1	0	2	3
Mood altered	<1	1	1	2
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	<1	0	1	1
Epistaxis	0	1	1	0
Skin and subcutaneous tissue disorders				
Pruritus	1	3	2	3
Hyperhidrosis	<1	0	1	2

Table 3 - Incidence of Most Common Dose-Related Treatment-Emergent Adverse Events in Double-Blind, Placebo-Controlled Adjunctive Therapy Partial-Onset Seizure Trials (Events ≥1% of Patients in the total VIMPAT group and More Frequent Than in the Placebo Group)

MedDRA Preferred Term	Placebo N=364 %	200 g/day N=270 %	400 g/day N=471 %	600 g/day N=203 %
Diplopia	2	6	10	16
Vision blurred	3	2	9	16
Nausea	4	7	11	17
Vomiting	3	6	9	16
Dizziness	8	16	30	53
Ataxia	2	4	7	15
Tremor	4	4	6	12
Nystagmus	4	2	5	10

Cardiac

Dose-dependent prolongations in PR interval with VIMPAT have been observed in clinical studies in patients and in healthy subjects (see 10.2 Pharmacodynamics, Cardiac Electrophysiology). In controlled adjunctive therapy clinical trials in patients with partial-onset seizures, asymptomatic first-degree AV block was observed as an adverse reaction in 0.4% (4/944) of patients randomized to receive VIMPAT and 0% (0/364) of patients randomized to receive placebo. In the controlled monotherapy clinical trial in patients with partial-onset seizures, first-degree AV block was reported in 1.6% (6/382) of VIMPAT-treated patients aged less than 65 years of age and in 4.8% (3/62) of VIMPAT-treated patients older than 65 years of age. In clinical trials in patients with diabetic neuropathy, asymptomatic first-degree AV block was observed as an adverse reaction in 0.6% (8/1393) of patients receiving VIMPAT and 0% (0/470) of patients receiving placebo. No second or higher degree AV block was seen in lacosamide treated epilepsy patients in controlled clinical trials. In clinical trials in patients with diabetic neuropathic pain, second-degree AV block has been rarely reported (<0.1%) (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular). However, cases with second and third degree AV block associated with lacosamide treatment have been reported in post-marketing experience (see 8.5 Post-Market Adverse Reactions, Cardiac disorders).

Syncope

In the monotherapy clinical trial comparing VIMPAT to carbamazepine (controlled release), syncope was reported in 7/444 (1.6%) VIMPAT treated patients and 1/442 (0.2%) carbamazepine (controlled-release) treated patients (see 7 WARNINGS AND PRECAUTIONS, Syncope).

Elderly

In the monotherapy study comparing VIMPAT to carbamazepine (controlled release), the safety profile of VIMPAT in elderly patients (≥ 65 years of age) appeared to be similar to that observed in patients less than 65 years of age. However, a higher incidence of fall (9.7% vs. 0.8%), diarrhea (6.5% vs. 1.3%) and tremor (6.5% vs. 0.3%) was reported in elderly patients compared to younger adult patients.

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/or 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
- **Investigations**: alanine aminotransferase increased
- **Nervous system disorders**: paresthesia, cerebellar syndrome

Intravenous Adverse Reactions

Adverse reactions with intravenous (IV) administration generally appeared similar to those observed with the oral formulation, although IV 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 150 mg VIMPAT. This patient was on a beta-blocker. Infusion was discontinued and the patient recovered.

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 Abuse and Dependence/Liability

Lacosamide showed no signs of abuse potential in three rat models. After prolonged administration to rats and dogs, there was no tolerance to lacosamide's pharmacological actions and abrupt cessation of treatment did not produce symptoms of psychological or physical dependence.

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. 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%.

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.

8.3 Less Common Clinical Trial Adverse Reactions

Other adverse events reported by <1% of patients with partial-onset seizures in the total VIMPAT group in placebo-controlled adjunctive therapy clinical trials that occurred more frequently than in the placebo group were:

Eye disorders: eye irritation

Nervous system disorders: hypokinesia

Vascular disorders: hot flush

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

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 ≥3x ULN (upper limit of normal) occurred in 0.7% (7/935) of VIMPAT patients and 0% (0/356) of placebo patients. One case of hepatitis with transaminases >20x 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.

8.5 Post-Market Adverse Reactions

Since the first global approval of VIMPAT on 29 August 2008 through 28 February 2018, there are approximately 1,424,796 patient-years of exposure to lacosamide. In addition to the adverse events reported during clinical studies and listed above, the following adverse events have been reported in post-marketing experience. Table 4 is based on post-market spontaneous adverse event reports. The percentages shown are calculated by dividing the number of adverse events reported to the company by the estimated number of patient years exposed to lacosamide. Because these adverse events are reported spontaneously from a population of uncertain size, it is not possible to reliably estimate their frequency. Furthermore, a causal relationship between lacosamide and the emergence of these events has not been clearly established.

Table 4 - Post-Market Spontaneous Adverse Event Reports

Adverse Events	Reported Frequency		
	Uncommon <1% and ≥0.1%	**Rare <0.1% and ≥0.01%**	**Very rare <0.01%**
Immune system disorders			
Drug hypersensitivity reactions			X
Multiorgan hypersensitivity reactions[1]			X
Blood and lymphatic system disorders			
Leukopenia			X
Thrombocytopenia			X
Agranulocytosis			X
Cardiovascular disorders			
Bradycardia			X
Atrioventricular block			X
Atrial fibrillation			X
Atrial flutter			X
Cardiac arrest			X
Cardiac failure			X
Myocardial infarction			X
Ventricular tachyarrhythmia			X
Hepatobiliary disorders			
Liver function test abnormal			X
Hepatic enzyme increased (> 2x ULN)			X
Hepatitis			X

Adverse Events	Reported Frequency		
	Uncommon <1% and ≥0.1%	**Rare <0.1% and ≥0.01%**	**Very rare <0.01%**
Metabolism and nutrition disorders			
Hyponatremia			X
Nervous system disorders			
Ataxia		X	
Syncope			X
Seizure	X		
Dyskinesia			X
Psychiatric disorders			
Euphoric mood			X
Suicide attempt			X
Suicidal ideation		X	
Aggression		X	
Agitation		X	
Psychotic disorder			X
Insomnia		X	
Hallucination		X	
Skin and subcutaneous tissue disorders			
Rash		X	
Angioedema			X
Urticaria			X
Stevens-Johnson Syndrome			X
Toxic Epidermal Necrolysis			X
Alopecia			X

[1] Includes related preferred term DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms)

Cardiac disorders

Second and third degree AV block, ventricular tachyarrhythmia, atrial fibrillation and atrial flutter associated with lacosamide treatment have been reported in post-marketing experience (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

Hepatic/Biliary/Pancreatic

Post-marketing reports of abnormal liver enzyme values, liver injury, acute hepatic failure (including hepatic encephalopathy and hepatic coma) and jaundice have been received in patients taking VIMPAT either alone, or in conjunction with other medications. Rare cases of clinically significant liver injury that were considered probably or possibly related to VIMPAT have been reported.

Nervous system disorders

Cases of seizure worsening (including occurrence of status epilepticus) have been reported. Post-market cases of dyskinesia have been reported in patients taking VIMPAT either alone, or in conjunction with other medications.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

VIMPAT should be used with caution in patients treated with medicinal products known to be associated with PR prolongation including sodium channel blocking antiepileptic drugs, pregabalin and beta-blockers, and in patients treated with antiarrhythmic drugs (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

In Vitro Assessment of Drug Interactions

In vitro metabolism studies indicate that lacosamide does not induce the enzyme activity of drug metabolizing cytochrome P450 isoforms CYP1A2, 2B6, 2C9, 2C19 and 3A4 at concentrations (12.5 µg/mL) close to the human peak plasma concentration (10.9 µg/mL, C_{max}, steady state at maximum recommended human dose (MRHD) of 400 mg/day). At concentrations 10 times higher (125 µg/mL), enzyme activities were less than 2-fold increased. Lacosamide did not inhibit CYP 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1, 3A4/5 at concentrations up to 1000-fold greater than the C_{max} for 400 mg/day. The inhibitory concentrations (IC_{50}) of CYP3A4, 3A5, 2C9 and 1A1 by lacosamide are at least 70-fold higher than the C_{max} for 400 mg/day.

In vitro data suggest that lacosamide has the potential to inhibit CYP2C19 at therapeutic concentrations (60% inhibition at 25µg/mL). However, an *in vivo* evaluation in healthy subjects

showed no inhibitory effect of lacosamide (600 mg/day administered as 300 mg BID dosing) on the single dose pharmacokinetics of omeprazole (40 mg).

Lacosamide is a CYP2C19 substrate. The relative contribution of other CYP isoforms or non-CYP enzymes in the metabolism of lacosamide is not clear.

Lacosamide was not a substrate or inhibitor for P-glycoprotein.

Since <15% of lacosamide is bound to plasma proteins, a clinically relevant interaction with other drugs through competition for protein binding sites is unlikely.

In Vivo Assessment of Drug Interactions

Drug-drug interaction studies in healthy subjects showed no pharmacokinetic interactions between VIMPAT and carbamazepine, valproic acid, digoxin, metformin, omeprazole, midazolam, 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 adjunctive therapy clinical trials in patients with partial-onset seizures.

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

9.4 Drug-Drug Interactions

Drug-Interaction Studies with Antiepileptic Drugs (AEDs)

- **Effect of VIMPAT on concomitant AEDs**

VIMPAT 400 mg/day had no influence on the pharmacokinetics of 600 mg/day valproic acid and 400 mg/day carbamazepine in healthy subjects.

The placebo-controlled adjunctive therapy clinical studies in patients with partial-onset seizures showed that steady-state plasma concentrations of levetiracetam, carbamazepine, carbamazepine epoxide, lamotrigine, topiramate, oxcarbazepine monohydroxy derivative (MHD), phenytoin, valproic acid, phenobarbital, gabapentin, clonazepam, and zonisamide were not affected by concomitant intake of VIMPAT at 200 to 600 mg/day.

- **Effect of concomitant AEDs on VIMPAT**

Drug-drug interaction studies in healthy subjects showed that 600 mg/day valproic acid had no influence on the pharmacokinetics of 400 mg/day VIMPAT. Likewise, 400 mg/day carbamazepine had no influence on the pharmacokinetics of VIMPAT (400 mg/day) in a healthy subject study. Population pharmacokinetics results in patients with partial-onset seizures showed small reductions (approximately 25% lower) in lacosamide plasma concentrations when VIMPAT (200 to 600 mg/day) was co-administered with carbamazepine, phenobarbital or phenytoin.

Drug-Drug Interaction Studies with Other Drugs

The drugs listed below are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

- **Digoxin**

VIMPAT (400 mg/day) did not affect pharmacokinetics of digoxin (0.5 mg once daily) in a study in healthy subjects. There was no effect of digoxin on the pharmacokinetics of VIMPAT.

- **Metformin**

There were no clinically relevant changes in metformin levels following co-administration of VIMPAT (400 mg/day). Metformin (500 mg three times a day) had no effect on the pharmacokinetics of VIMPAT (400 mg/day) in healthy subjects.

- **Midazolam**

Midazolam is a CYP3A4 substrate.

VIMPAT administered as a single 200 mg dose or repeated doses of 400 mg/day (200 mg BID) to healthy subjects had no clinically relevant effect on the AUC of midazolam, but slightly increased the C_{max} over time (30% after 13 days).

- **Omeprazole**

Omeprazole is a CYP2C19 substrate and inhibitor.

Omeprazole (40 mg once daily) increased the AUC of lacosamide by 19% (300 mg, single dose), which is unlikely to be clinically significant. Lacosamide (600 mg/day) did not affect the single-dose pharmacokinetics of omeprazole (40 mg) in healthy subjects.

- **Oral Contraceptives**

In an interaction trial in healthy subjects, there was no clinically relevant interaction between lacosamide (400 mg/day) and the oral contraceptives ethinylestradiol (0.03 mg) and levonorgestrel (0.15 mg). Progesterone concentrations were not affected when the medicinal products were co-administered (see 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential).

- **Warfarin**

Co-administration of warfarin as a single 25 mg dose with lacosamide 400 mg/day (200 mg BID) to healthy subjects had no clinically relevant change in the pharmacokinetics and pharmacodynamics of warfarin.

9.5 Drug-Food Interactions

VIMPAT is completely absorbed after oral administration. Food does not affect the rate or extent of absorption.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been evaluated.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been observed.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The precise mechanism by which lacosamide exerts its antiepileptic effect in humans is unknown (see **Preclinical Pharmacology** for experimental *in vitro* and *in vivo* data in animals).

Preclinical Pharmacology

In vitro electrophysiological studies have shown that lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in reduced hyperexcitability of neuronal membranes and inhibition of repetitive neuronal firing.

Lacosamide protected against seizures in a broad range of rodent models (mice and rats) of partial and primary generalized seizures and delayed kindling development. In non-clinical experiments lacosamide in combination with levetiracetam, carbamazepine, phenytoin, valproate, lamotrigine, topiramate or gabapentin showed synergistic or additive anticonvulsant effects. Lacosamide was not effective in the rat WAG/rij model of absence epilepsy and caused mild dose-dependent increases in the number of characteristic EEG spike wave discharges for one hour after single intraperitoneal doses of 3-30 mg/kg. A similar phenomenon also occurs in WAG/rij rats given the other antiepileptic drugs phenytoin and carbamazepine.

A safety pharmacology study with intravenous (IV) administration of lacosamide at doses of 2-12 mg/kg in anesthetized beagle dogs showed transient increases in PR interval and QRS complex duration and decreases in blood pressure most likely due to a cardiodepressant action as indicated by decreases in cardiac output. There was evidence of a dose relationship. One high dose dog (12 mg/kg) died due to a marked and sustained drop in blood pressure followed by cardiac arrest. At the low dose, these transient changes started in the same plasma lacosamide concentration range as after maximum recommended clinical dosing (300 mg BID). Progressively reduced systolic, diastolic, and mean arterial blood pressure was also seen in anesthetized Cynomolgus monkeys given up to 4 sequential IV lacosamide doses of 15 mg/kg. In anesthetized dogs given IV doses of 15-45 mg/kg (given as 1 to 3 sequential doses) and

anaesthetized monkeys given IV doses of 30-120 mg/kg (given as 1 to 4 sequential doses), slowing of atrial and ventricular conductivity, atrioventricular block and atrioventricular dissociation were seen. In an *in vitro* assay conducted in HEK293 cells that stably express the human-ether-à-go-go related gene (hERG), a weak 7% inhibition of hERG current was seen only at the highest concentration (3000 µmol/L) tested. This is consistent with the absence of changes in QT interval in safety pharmacology studies conducted in dogs and monkeys.

10.2 Pharmacodynamics

A pharmacokinetic-pharmacodynamic (efficacy) analysis was performed based on the pooled data from the 3 controlled adjunctive therapy efficacy trials for partial-onset seizures. Lacosamide exposure is correlated with the reduction in seizure frequency. However, in group analyses, doses above 400 mg/day, when administered as adjunctive therapy, do not appear to confer additional benefit and are associated with more severe and substantially higher frequency of adverse reactions.

Cardiac Electrophysiology

Electrocardiographic effects of VIMPAT (lacosamide) were determined in a double-blind, randomized clinical pharmacology ECG trial of 247 healthy subjects. Chronic oral doses of 400 and 800 mg/day were compared with placebo and a positive control (400 mg moxifloxacin). VIMPAT did not prolong QTc interval and did not have a dose-related or clinically important effect on QRS duration. VIMPAT produced a dose-related increase in mean PR interval. At steady-state, the time of the maximum observed mean PR interval corresponded with t_{max}. The placebo-subtracted maximum increase in PR-interval (at t_{max}) was 7.3 ms for the 400 mg/day group and 11.9 ms for the 800 mg/day group.

For patients with partial-onset seizures who participated in the controlled adjunctive therapy trials, the placebo-subtracted maximum increase in PR interval for a 400 mg/day VIMPAT dose was 3.1 ms. For patients with diabetic neuropathic pain who participated in controlled trials, the placebo-subtracted maximum increase in PR-interval for a 400 mg/day VIMPAT dose was 8.3 ms (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular and 8.2 Clinical Trial Adverse Reactions, Cardiac).

10.3 Pharmacokinetics

The pharmacokinetics of VIMPAT has been studied in healthy adult subjects (age range 18 to 87), adults with partial-onset seizures, adults with diabetic neuropathy, and subjects with renal and hepatic impairment. A summary of lacosamide's pharmacokinetic parameters in healthy subjects is provided in Table 5.

Lacosamide is completely absorbed after oral administration with negligible first-pass effect with a high absolute bioavailability of approximately 100%. The maximum lacosamide plasma

concentrations occur approximately 0.25 to 4 hours post-dose after oral dosing, and elimination half-life is approximately 13 hours. Steady state plasma concentrations are achieved after 3 days of twice daily repeated administration. Pharmacokinetics of lacosamide is dose proportional (100-800 mg) and time invariant, with low inter- and intra-subject variability. Compared to lacosamide, the major metabolite, O-desmethyl metabolite, has a longer T_{max} (0.5 to 12 hours) and elimination half-life (15-23 hours) but has no known pharmacologic activity.

Table 5 - Summary of lacosamide Pharmacokinetic Parameters in Healthy Subjects

	C_{max} (µg/mL) Arithmetic Mean	T_{max} Median (range)	$t_{½}$ (h) Arithmetic Mean	AUC_T (µg/mL*h) Arithmetic Mean
Oral tablet 200mg	5.03	0.75 (0.25-4.00)	13.96	88.61
IV solution for injection 200mg (duration 30 minutes)	5.96	0.50 (0.50-2.00)	12.00	80.24
IV solution for injection 200mg (duration 60 minutes)	5.38	1.00 (1.00-3.00)	12.00	81.16

Absorption

Lacosamide is rapidly and completely absorbed after oral administration. The oral bioavailability of lacosamide tablets is approximately 100%. Following oral administration, the plasma concentration of unchanged lacosamide increases rapidly and reaches C_{max} about 0.25 to 4 hours post-dose. Food does not affect the rate and extent of absorption.

After IV administration (30-60 minutes), C_{max} is reached at the end of infusion. The plasma concentration increases proportionally with dose after oral (100-800 mg) and IV (50-300 mg) administration.

Distribution

The volume of distribution is approximately 0.6 L/kg. Lacosamide is less than 15% bound to plasma proteins.

Metabolism

The metabolism of lacosamide has not been completely characterized. Approximately 95% of the dose is excreted in the urine as drug and metabolites. The major compounds excreted in urine are unchanged lacosamide (approximately 40% of the dose) and its O-desmethyl metabolite, which has no known pharmacological activity (less than 30%). A structurally unknown polar fraction (about 20%) was also found in urine, but was detected only in small amounts (0-2%) in human plasma of some subjects. Small amounts (0.5-2%) of additional metabolites were also found in the urine. The plasma exposure of the major human metabolite (AUC), O-desmethyl-lacosamide, is approximately 15% of the drug product, lacosamide.

CYP2C19, CYP2C9 and CYP3A4 are mainly responsible for the formation of the O-desmethyl metabolite. However, no clinically relevant difference in lacosamide exposure was observed comparing its pharmacokinetics in extensive metabolisers (EMs, with a functional CYP2C19) and poor metabolisers (PMs, lacking a functional CYP2C19). Furthermore, an interaction trial with omeprazole (CYP2C19-inhibitor) demonstrated no clinically relevant changes in lacosamide plasma concentrations indicating that the importance of this pathway is minor. No other enzymes have been identified to be involved in the metabolism of lacosamide.

Elimination

Lacosamide is primarily eliminated from the systemic circulation by renal excretion and biotransformation. After oral and IV administration of 100 mg radiolabeled lacosamide, approximately 95% of radioactivity administered was recovered in the urine and less than 0.5% in the feces. The elimination half-life of the unchanged drug is approximately 13 hours and is not altered by different doses, multiple dosing or IV administration. The pharmacokinetics are dose-proportional and time-invariant, with low intra- and inter-subject variability. Following twice daily dosing, steady state plasma concentrations are achieved after a 3 day period. The plasma concentration increases with an accumulation factor of approximately 2.

Special Populations and Conditions

- **Pediatrics (<18 years of age):** Pharmacokinetics of lacosamide have not been established in pediatric patients.
- **Geriatrics (≥ 65 years of age):** In a study in elderly men and women, the AUC was about 30 and 50% increased compared to young men, respectively. This is partly related to lower body weight. The body weight normalized difference is 26 and 23%, respectively. An increased variability in exposure was also observed. The renal clearance of lacosamide was only slightly reduced in elderly subjects in this study.
- **Sex:** VIMPAT clinical trials indicate that gender does not have a clinically relevant influence on the pharmacokinetics of VIMPAT.
- **Genetic Polymorphism:** There are no clinically relevant differences in the pharmacokinetics of lacosamide between CYP2C19 poor metabolizers and extensive metabolizers. Results

from a trial in poor metabolizers (PM) (N=4) and extensive metabolizers (EM) (N=8) of cytochrome P450 (CYP) 2C19 showed that lacosamide plasma concentrations were similar in PMs and EMs, but plasma concentrations and the amount excreted into urine of the O-desmethyl metabolite were about 70% reduced in PMs compared to EMs.

- **Ethnic Origin:** Approximately 90% of the patient population in epilepsy trials was Caucasian. There are no clinically relevant differences in the pharmacokinetics of VIMPAT between Asian, Black, and Caucasian subjects.
- **Hepatic Insufficiency:** Lacosamide undergoes metabolism. Subjects with moderate hepatic impairment (Child-Pugh B) showed higher plasma concentrations of lacosamide (approximately 50-60% higher AUC compared to healthy subjects). A maximum dose of 300 mg/day is recommended for patients with mild to moderate hepatic impairment. Patients with mild to moderate hepatic impairment should be titrated with caution and observed closely during dose titration. Patients with co-existing hepatic and renal impairment of any degree should also be monitored closely during dose titration.

  The pharmacokinetics of lacosamide have not been evaluated in patients with severe hepatic impairment. VIMPAT use in patients with severe hepatic impairment is not recommended (see 4.2 Recommended Dose and Dosage Adjustment, Patients with Hepatic Impairment) and 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency).
- **Renal Insufficiency:** Lacosamide and its major metabolite are eliminated from the systemic circulation primarily by renal excretion.

  The AUC of lacosamide was increased approximately 25% in mildly (CL_{CR} 50-80 mL/min) and moderately (CL_{CR} 30-50 mL/min), and 60% in severely (CL_{CR}≤30mL/min) renal-impaired patients compared to subjects with normal renal function (CL_{CR}>80mL/min), whereas C_{max} was unaffected. No dose adjustment is considered necessary in mildly and moderately renal impaired subjects. A maximum dose of 300 mg/day is recommended for patients with severe renal impairment (CL_{CR}≤30mL/min) and in patients with endstage renal disease.

  Hemodialysis

  Lacosamide 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.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15 – 30°C).

VIMPAT solution for injection was found to be physically compatible and chemically stable when mixed with diluents (see 4.3 Reconstitution) for at least 24 hours and stored in glass or polyvinyl chloride (PVC) bags at room temperature 15-30°C.

The stability of VIMPAT solution for injection in other infusion solutions has not been evaluated.

Any unused portion of VIMPAT solution for injection should be discarded.

12 SPECIAL HANDLING INSTRUCTIONS

No Special Handling Instructions are required for this drug product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

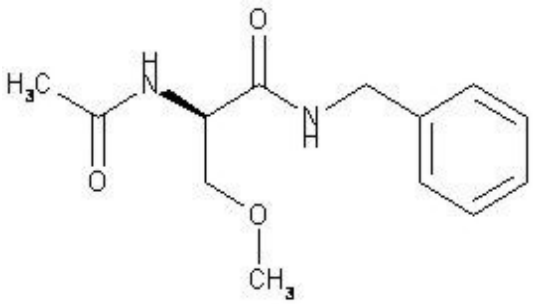
Drug Substance

Proper name: lacosamide

Chemical name: (R)-2-acetamido-N-benzyl-3-methoxypropionamide (IUPAC)

Molecular formula and molecular mass: $C_{13}H_{18}N_2O_3$, 250.30

Structural formula:



Physicochemical properties: Lacosamide is a white to light yellow powder. It is sparingly soluble in water and slightly soluble in acetonitrile and ethanol. The melting point of lacosamide is between 140°C and 146°C. The specific optical rotation of lacosamide in methanol at 25°C is between +14 and +18.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Monotherapy

Table 6 - Summary of patient demographics for clinical trials in epilepsy (Monotherapy)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Monotherapy Study (SP0993)	Phase 3, multicenter, double-blind, double-dummy, randomized, positive-controlled, non-inferiority	VIMPAT: 200, 400, 600mg/day Carbamazepine (controlled release): 400, 800, 1200mg/day oral Up to 121 weeks Up-titration and Stabilization Phase: 3 weeks Evaluation Phase: 26 weeks Maintenance Phase: 26 weeks End of Study Phase (includes End of Taper Visit and Final Visit): up to 7 weeks (taper over 1, 3 or 5 weeks for starting dose of 200mg, 400mg or 600mg/day, respectively)	886	41.8 years (16 – 87)	475 M 411 F

The efficacy of VIMPAT as monotherapy in partial-onset seizures was established in study SP0993 in which 444 patients received VIMPAT or controlled-release carbamazepine (n=442). Only patients with newly or recently diagnosed epilepsy participated in this study. Patients had to present with at least two seizures occurring in the last 12 months prior to study entry. Patients previously treated chronically (> 2 weeks) for epilepsy with any AED in the last 6 months before study entry were not permitted in the study. A total of 27 pediatric and 62 elderly patients took at least one dose of VIMPAT 200 - 600 mg/day. In the elderly patient

population, the maintenance VIMPAT dose was 200 mg/day in 55 patients (88.7%), 400 mg/day in 6 patients (9.7%) and the dose was escalated to 600 mg/day in 1 patient (1.6%).

The step-wise design for the study employed 3 predefined target dose levels for both VIMPAT and carbamazepine (controlled release). Patients initiated treatment with VIMPAT 100 mg/day or carbamazepine (controlled release) 200 mg/day and study medication was subsequently up-titrated to the first target therapeutic dose level of VIMPAT 200 mg/day or carbamazepine (controlled release) 400 mg/day. In case this dose did not control seizures during the 6-month Evaluation Phase of the study, the dose was increased to VIMPAT 400 mg/day or carbamazepine (controlled release) 800 mg/day, and if this dose did not control seizures, the dose was increased to VIMPAT 600 mg/day or carbamazepine (controlled release) 1200 mg/day. Following the Evaluation Phase at a specific dose, patients who had remained seizure-free, were entered into the Maintenance Phase.

The study completion rates were 66.9% (n=210) for the VIMPAT 200 mg/day dose level, 47.1% (n=41) for the 400 mg/day dose level and 34.9% (n=15) for the 600 mg/day dose level. Approximately 95% of the patients, who completed the 6-month Evaluation Phase and remained seizure free, received daily VIMPAT doses of 200 or 400 mg. In the study, 19 patients received 600 mg/day and remained seizure free.

The primary efficacy variable was the proportion of patients remaining seizure free for 6 consecutive months (26 consecutive weeks) of treatment following stabilization at the last evaluated dose for each patient.

Study Results

VIMPAT met the pre-defined non-inferiority criteria and was considered to be non-inferior to carbamazepine (controlled release) based on the primary efficacy end-point.

Among the total of all VIMPAT-treated patients (n=444), approximately 56% (n=249), 13%, (n=59) and 4% (n=19) completed the 6-month Evaluation Phase and remained seizure free at the last evaluated VIMPAT dose of 200 mg/day, 400 mg/day, and 600 mg/day, respectively.

The number and percentage of patients who completed the 6-month seizure freedom Evaluation Phase and remained seizure free during this period are presented by treatment group overall and by the last evaluated dose in Table 7 below. Overall, the proportion of patients who completed 6 months and remained seizure free at the last dose level was similar between the VIMPAT (73.6%) and carbamazepine (controlled release) (69.7%) treatment groups.

Table 7 - Number and Percentage of Epilepsy Patients who Completed 6 Month Evaluation Phase and Remained Seizure Free at the Last Evaluated Dose based on Full Analysis Set (Monotherapy)

Last evaluated dose level	6-months	
Parameter	VIMPAT	CBZ-CR
Overall, n	444	442
Seizure free for 6 months, n (%)	327 (73.6)	308 (69.7)
Dose level 1, n	314	324
Seizure free for 6 months, n (%)	249 (79.3)	235 (72.5)
Dose level 2, n	87	85
Seizure free for 6 months, n (%)	59 (67.8)	60 (70.6)
Dose level 3, n	43	33
Seizure free for 6 months, n (%)	19 (44.2)	13 (39.4)

CBZ-CR=carbamazepine (controlled release)
Note: Dose level 1=VIMPAT 200mg/day or CBZ-CR 400mg/day; Dose level 2=VIMPAT 400mg/day or CBZ-CR 800mg/day; Dose level 3=VIMPAT 600mg/day or CBZ-CR 1200mg/day.

Other efficacy end-points such as estimates of 12-month seizure freedom rates were supportive of the primary efficacy end-point.

The 6-month seizure freedom rates observed in patients aged 65 years or older were similar between both treatment groups and in the overall patient population.

Adjunctive Therapy

Table 8 - Summary of patient demographics for clinical trials in epilepsy (Adjunctive Therapy)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Study 1 (SP667 Adjunctive Therapy)	Phase 2b, multicentre, double-blind, randomized, placebo-controlled, parallel group	VIMPAT: 200, 400, 600mg/day Placebo oral Up to 29 weeks Baseline: 8 weeks Titration Phase: 6 weeks Maintenance Phase: 12 weeks Transition Phase: 2 weeks or Taper Phase: 3 weeks	418	39.9 years (18 – 68)	191 M 227 F
Study 2 (SP754 Adjunctive Therapy)	Phase 3, multicentre, double-blind, randomized, placebo-controlled, parallel group	VIMPAT: 400, 600 mg/day Placebo oral Up to 29 weeks Baseline: 8 weeks Titration Phase: 6 weeks Maintenance Phase: 12 weeks Transition Phase: 2 weeks or Taper Phase: 3 weeks	405	38.3 years (16 – 71)	200 M 205 F

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Study 3 (SP755 Adjunctive Therapy)	Phase 3, multicentre, double-blind, randomized, placebo-controlled, parallel group	VIMPAT: 200, 400 mg/day Placebo oral Up to 26 weeks Baseline: 8 weeks Titration Phase: 4 weeks Maintenance Phase: 12 weeks Transition Phase or Taper Phase: 2 weeks	485	37.8 years (16 -70)	250 M 235 F

The efficacy of VIMPAT as adjunctive therapy in partial-onset seizures was established in three 12-week, randomized, double-blind, placebo-controlled, multicenter trials involving 944 adult patients that were randomized to receive lacosamide (and 364 adult patients that were randomized to placebo). Patients had partial-onset seizures with or without secondary generalization and were not adequately controlled with 1 to 3 concomitant AEDs. During an 8-week baseline period, patients were required to have an average of ≥4 partial-onset seizures per 28 days with no seizure-free period exceeding 21 days. In these 3 trials, patients had a mean duration of epilepsy of 24 years and a median baseline seizure frequency ranging from 10 to 17 per 28 days. A total of 10 patients aged 16 to 17 years were enrolled in the trials. Overall, 84% of patients were taking 2 to 3 concomitant AEDs. Of these patients, 18% were also receiving concurrent vagal nerve stimulation (VNS).

Study 1 compared doses of VIMPAT 200, 400, and 600 mg/day and placebo in 107, 108, 106, and 97 randomized patients, respectively. Study 2 compared doses of VIMPAT 400 and 600 mg/day and placebo in 204, 97, and 104 randomized patients, respectively. Study 3 compared doses of VIMPAT 200 and 400 mg/day and placebo in 163, 159, and 163 randomized patients, respectively. Following the 8-week Baseline Phase, patients were randomized and up-titrated by initiating treatment at 100 mg/day (50 mg BID), and increased in weekly increments of 100 mg/day to the target dose (a 1-step back-titration of VIMPAT 100 mg/day or placebo was allowed in the case of intolerable adverse events at the end of the Titration Phase). Following the Titration Phase, patients received a stable dose of VIMPAT for 12 weeks (Maintenance Phase). Among the patients randomized to VIMPAT, 76% completed the Treatment Phase (Titration and Maintenance).

The primary efficacy end-point in all three trials was the reduction in seizure frequency per 28 days from Baseline to the Maintenance Phase in VIMPAT arm(s) as compared to placebo. The 50% responder rate (percent of patients with at least 50% reduction in seizure frequency from Baseline to the Maintenance Phase) as compared to placebo was a secondary endpoint.

Two trials were conducted in patients with partial-onset seizures using VIMPAT solution for injection. These trials were designed to identify the appropriate infusion duration(s) for VIMPAT solution for injection as a short-term replacement for VIMPAT tablets and to provide data to support the safety of infusion rates including 30 and 60 minutes. A total of 199 patients with partial-onset seizures were exposed to VIMPAT solution for injection.

Study Results

A statistically significant effect (in the reduction of seizure frequency from Baseline to the Maintenance Phase) was observed with VIMPAT doses of 200 mg/day (Study 3), 400 mg/day (Studies 1, 2, and 3), and 600 mg/day (Studies 1 and 2). The 50% responder rates for VIMPAT doses of 400 mg and 600 mg/day were also statistically significant compared to placebo (see Table 9).

Table 9 - Median Percent Reduction in Partial Seizure Frequency per 28 days and 50% Responder Rates from Baseline to the Maintenance Phase (ITT Population) (Adjunctive Therapy)

			AED's + VIMPAT (mg/day)		
Study	**Efficacy results**	**AED's + Placebo**	**200**	**400**	**600**
1	N	96	107	107	105
	Median % Reduction	10%	26%	39%**	40%**
	50% Responders	21.9%	32.7%	41.1%**	38.1%*
2	n	104	--	201	97
	Median % Reduction	20.8%	--	37.3%**	37.8%**
	50% Responders	18.3%	--	38.3%**	41.2%**
3	n	159	160	158	--
	Median % Reduction	20.5%	35.3%*	36.4%*	--
	50% Responders	25.8%	35.0%	40.5%**	--

ITT=intent to treat

*Significant at the 0.05 level; ** Significant at the 0.01 level.

Significance reflects the percent reduction over placebo which is based on log-transformed seizure frequency from pairwise treatment analysis of covariance (ANCOVA) models with terms for treatment, pooled site, and the baseline period measurement and pairwise treatment logistic regression models with terms for treatment and pooled site.

A statistically significant reduction in seizure frequency from Baseline to the Treatment Phase (i.e. Titration Phase + Maintenance Phase) was also observed with VIMPAT doses of 200 mg/day (Study 3), 400 mg/day (Studies 1, 2, and 3), and 600 mg/day (Studies 1 and 2) compared to placebo. The 50% responder rates for VIMPAT doses of 400 mg and 600 mg/day were also statistically significant compared to placebo.

There were no significant differences in seizure control as a function of gender. Data on race were limited (8.3% of the patients were non-Caucasian).

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

In the toxicity studies, the plasma concentrations of lacosamide obtained were similar or only marginally higher than those observed in patients, which leaves low or non-existing margins to human exposure.

- **Acute Toxicity**

Results from acute oral dose toxicity studies with lacosamide indicate a no-observed-effect-level (NOEL) of 31.6 mg/kg in both mice and rats. The estimated LD_{50} values were 383 and 253 mg/kg for mice and rats, respectively. After intravenous administration the NOELs were 10 and 25 mg/kg and the estimated LD_{50} values were 178 and >100 mg/kg for mice and rats, respectively. In acute toxicity studies, clinical signs at high doses included exaggerated pharmacodynamic effects of lacosamide on the central nervous system (CNS) such as reduced motility, ataxia, abdominal/lateral position, loss of righting reflex, reduced muscle tone, hind limb weakness, tremor, dyspnea and convulsions.

- **Long Term Toxicity**

In repeated oral dose studies, lacosamide caused convulsions in mice, rats, rabbits, and dogs after oral dosing at C_{max} exposures generally only slightly higher than the C_{max} at steady state of 14.5 µg/mL after the maximum recommended human dose of 300 mg BID in patients. The C_{max} ratios were as low as 3.4 in mice, 1.1 in rats, 1.8 in rabbits, and 1.4 in adult and juvenile dogs at the lowest dose causing convulsions and as low as 1.9 in mice, less than 1.1 in rats, 0.9 in rabbits, 1.0 in adult dogs, and 0.6 in juvenile dogs at the highest dose level not associated with convulsions. The convulsions usually occurred in the context of other significant clinical signs including one or more of tremors, ataxia, hypoactivity, and recumbency, which also occurred at

dose levels not associated with convulsions.

Consistent with the safety pharmacology studies, lacosamide caused 13%-37% decreases in systolic blood pressure in females in the 12 month chronic dog toxicity study at dose levels of 10-25 mg/kg/day with the C_{max} at 10 mg/kg equivalent to that of humans given the maximum recommended dose of 300 mg BID.

In the repeated dose toxicity studies, mild reversible liver changes were observed in rats starting at about 2 times the clinical exposure. These changes included an increased organ weight, hypertrophy of hepatocytes, increases in serum concentrations of liver enzymes and increases in total cholesterol and triglycerides. Apart from the hypertrophy of hepatocytes, no other histopathologic changes were observed.

Carcinogenesis and Mutagenesis

There was no evidence of drug related carcinogenicity in mice or rats. Mice and rats received lacosamide once daily by oral administration for 104 weeks at doses producing plasma exposures (AUC) up to approximately 1 and 2.3 times, respectively, the plasma AUC in humans at the maximum recommended human dose (MRHD) of 600 mg/day.

Lacosamide was negative in an *in vitro* Ames test and an *in vivo* mouse micronucleus assay and an *in vivo* unscheduled DNA synthesis (UDS) test. In the *in vivo* tests, plasma exposures (AUC) correspond to up to approximately 3 times the plasma AUC in humans at the maximum recommended human dose (MRHD) of 600 mg/day. Lacosamide induced a positive response in the *in vitro* mouse lymphoma assay at excessively high concentrations (i.e. at concentrations above the maximum recommended concentration of 10 mM).

Reproductive and Developmental Toxicology

In reproductive and developmental toxicity studies in rodents and rabbits, no teratogenic effects but an increase in numbers of stillborn pups and pup deaths in the peripartum period, and slightly reduced live litter sizes and pup body weights were observed at maternal toxic doses in rats corresponding to clinically relevant plasma exposure levels. Since higher exposure levels could not be tested in animals due to maternal toxicity, data are insufficient to fully characterize the embryofetotoxic and teratogenic potential of lacosamide. Studies in pregnant rats revealed that lacosamide and/or its metabolites readily crossed the placental barrier.

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 relevance of these observations remains equivocal. However, potential adverse effects on CNS development cannot be ruled out. 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 0.4 times that in humans at the MRHD of 600 mg/day.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrVIMPAT®

lacosamide tablets
lacosamide injection

Read this carefully before you start taking **VIMPAT** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **VIMPAT**.

What is VIMPAT used for?

VIMPAT is used in adults to treat partial-onset seizures and can be taken alone or with other seizure medicines.

How does VIMPAT work?

VIMPAT works in the brain to block the spread of seizure activity. The precise way that VIMPAT works to treat partial-onset seizures is unknown.

What are the ingredients in VIMPAT?

Medicinal ingredient: lacosamide

Non-medicinal ingredients:

Film-coated tablets: colloidal silicon dioxide, crospovidone, hydroxypropylcellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide and additional agents listed below:

50 mg tablets: black iron oxide, FD&C Blue #2/indigo carmine aluminum lake, red iron oxide
100 mg tablets: yellow iron oxide
150 mg tablets: black iron oxide, red iron oxide, yellow iron oxide
200 mg tablets: FD&C Blue #2/indigo carmine aluminum lake

Solution for injection: hydrochloric acid, sodium chloride and water for injection.

VIMPAT comes in the following dosage forms:

Film-coated tablets: 50 mg, 100 mg, 150 mg and 200 mg

Solution for injection: 10 mg/mL

Do not use VIMPAT if you:

- are allergic to lacosamide or any of the other ingredients in VIMPAT
- suffer or have suffered in the past from a certain type of heart rhythm disorder (second or third degree AV block)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take VIMPAT. Talk about any health conditions or problems you may have, including if you:

- have any health problems, including ones you have had in the past
- have kidney or liver disease
- suffer from a severe heart disease such as heart rhythm disorder, heart failure or heart attack
- are pregnant or plan to become pregnant. It is not known if VIMPAT may harm your unborn baby. You and your healthcare professional will have to decide if VIMPAT is right for you while you are pregnant. If you use VIMPAT while you are pregnant, ask your healthcare professional about joining the North American Antiepileptic Drug Pregnancy Registry by calling (888) 233-2334 (toll free). Women who are pregnant and planning to take VIMPAT should call the pregnancy registry to enable collection of valuable data about VIMPAT use in pregnancy. Information on the registry can also be found at the following website: http://www.aedpregnancyregistry.org/
- are breastfeeding. VIMPAT passes into breast milk and may harm your baby. You and your healthcare professional should decide whether you should take VIMPAT or breastfeed, but not both.

Other warnings you should know about:

Severe Skin Reactions: In rare cases, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Stevens - Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), has been reported with VIMPAT. These serious and life-threatening reactions have been reported in very rare cases with this type of medicine.

Driving and Using Machines: VIMPAT may cause dizziness and poor coordination which could increase the risk of accidental injury or a fall. Therefore, you should be careful until you are used to the effects this medicine might have.

Do not

- drive,
- operate complex machinery, or
- engage in other hazardous activities

until you know how VIMPAT affects you.

Ask your healthcare professional when it is okay to do these activities.

Visual Trouble: VIMPAT may cause double vision and blurred vision. If you experience visual disturbances while taking VIMPAT, notify your healthcare professional.

Suicidal Thoughts and Behaviour Changes: A small number of people being treated with anti-epileptics such as VIMPAT have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your healthcare professional.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with VIMPAT:

- any medicines that make you sleepy or dizzy.
- any medications to treat a heart condition, such as certain types of irregular heartbeat or heart failure (beta-blockers, class I anti-arrhythmic drugs, etc.).
- any medications that may cause certain changes in heart electrical activity (carbamazepine, pregabalin, lamotrigine, eslicarbazepine, etc.).

How to take VIMPAT:

VIMPAT Film-coated tablets

- VIMPAT may be taken with or without food.
- Swallow the tablets whole with plenty of water. Do not chew or crush tablets.

VIMPAT Solution for injection

The solution for injection is another way to give VIMPAT for a short time, up to 5 days, when it can't be taken by mouth. VIMPAT will be given into a vein (intravenously) by a healthcare professional.

Usual Dose:

VIMPAT must be taken twice a day, once in the morning and once in the evening, at about the same time each day.

When you take VIMPAT on its own

The treatment with VIMPAT usually starts with 100 mg in the morning and 100 mg in the evening (200 mg a day). After one week your dose may be increased. The daily maintenance dose is between 200 mg and 600 mg.

When you take VIMPAT with other seizure medicines

The treatment with VIMPAT usually starts with 50 mg in the morning and 50 mg in the evening (100 mg a day). After one week your dose may be increased. The daily maintenance dose is between 200 mg and 400 mg.

Your healthcare professional may use a different dose if you have problems with your kidneys or liver.

If your healthcare professional decides to stop your treatment with VIMPAT, he/she will decrease the dose step by step. This is to prevent your symptoms from coming back again or becoming worse.

Do not stop taking VIMPAT or any other seizure medicine unless your healthcare professional told you to. Stopping a seizure medicine is very serious and can cause seizures that will not stop (status epilepticus).

Tell your healthcare professional if your seizures get worse or if you have any new types of seizures.

Remember: This medicine has been prescribed for you. Do not give it to anybody else.

Overdose:

If you think you, or a person you are caring for, have taken too much VIMPAT, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose by a few hours, take it as soon as you remember. If it is close to your next dose, take VIMPAT at your next regular time. Do not take two doses at the same time to make up for the missed dose.

What are possible side effects from using VIMPAT?

These are not all the possible side effects you may have when taking VIMPAT. If you experience any side effects not listed here, tell your healthcare professional.

The most common side effects associated with the use of VIMPAT are:

- dizziness
- poor coordination
- headache

- nausea, vomiting
- fatigue
- blurred vision, double vision

If you are elderly (older than 65), you may have a higher chance of the following side effects:

- falling
- diarrhea
- tremors/shaking

Tell your healthcare professional about any side effect that bothers you or that does not go away.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Allergic reaction: swelling in the mouth, tongue, face and throat, itching, rash			✓
Heart rhythm problems: irregular pulse, slow pulse, rapid pulse, palpitations, shortness of breath, feeling lightheaded, fainting			✓
Thoughts of suicide or hurting yourself			✓
RARE			
Liver disorder or liver injury: itching, right upper belly pain, dark urine, yellow skin or eyes, unexplained flu-like symptoms			✓
Serious skin reaction: fever, severe rash, swollen lymph glands, flu-like feeling, blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body, yellow skin or eyes, shortness of breath, dry cough, chest pain or			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
discomfort, feeling thirsty, urinating less often, less urine			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store VIMPAT at room temperature, 15 to 30°C.
- Keep VIMPAT and all medicines out of the reach and sight of children.

If you want more information about VIMPAT:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.ucb-canada.ca, or by calling 1-866-709-8444.

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