

DATA SHEET

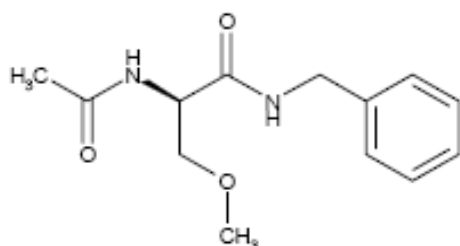
VIMPAT (lacosamide) film-coated tablets and injection

NAME OF THE MEDICINE

VIMPAT[®] (lacosamide)
50 mg, 100 mg, 150 mg and 200 mg film-coated tablets
200 mg/20 mL injection

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

Chemical structure:



Molecular formula: C₁₃H₁₈N₂O₃

MW: 250.30

CAS number: [175481-36-4]

DESCRIPTION

The active ingredient lacosamide is a white to light yellow powder. It is sparingly soluble in water (30 mg/mL at 25°C) and slightly soluble in acetonitrile and ethanol.

Film-coated tablets

Vimpat film-coated tablets contain the following inactive ingredients: colloidal anhydrous silica, crospovidone, hydroxypropylcellulose, hypromellose, lecithin, magnesium stearate, macrogol 3350, microcrystalline cellulose, polyvinyl alcohol, purified talc, titanium dioxide and dye pigments as specified below:

- 50 mg tablets: iron oxide red C177491, iron oxide black C177499, indigo carmine C173015
100 mg tablets: iron oxide yellow C177492
150 mg tablets: iron oxide yellow C177492, iron oxide red C177491, iron oxide black C177499
200 mg tablets: indigo carmine C173015

Injection

Vimpat injection is a clear, colourless, sterile solution containing 10 mg lacosamide per mL. The inactive ingredients are sodium chloride and water for injections. Hydrochloric acid is used to adjust the pH to 4.0.

PHARMACOLOGY

Mechanism of action

The precise mechanism by which lacosamide exerts its antiepileptic effect in humans remains to be fully elucidated. *In vitro* electrophysiological studies have shown that lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes.

Pharmacodynamic effects

Lacosamide protected against seizures in a broad range of animal models of partial and primary generalized seizures and delayed kindling development. In animal models for status epilepticus lacosamide displayed acute antiseizure effects, reduced the severity of chronic seizures and showed neuroprotection. In non-clinical experiments lacosamide in combination with levetiracetam, carbamazepine, phenytoin, valproate, lamotrigine, topiramate or gabapentin showed synergistic or additive anticonvulsant effects.

Cardiac Electrophysiology

Electrocardiographic effects of VIMPAT were determined in a double-blind, randomized clinical pharmacology 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 small, 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 who participated in the controlled trials, the placebo-subtracted mean maximum increase in PR interval for a 400 mg/day VIMPAT dose was 3.1 ms in patients with partial-onset seizures and 9.4 ms for patients with diabetic neuropathy.

Pharmacokinetic properties

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 0.5 to 4 hours post-dose. Food does not affect the rate and extent of absorption.

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

95% of the dose is excreted in the urine as drug and metabolites. The metabolism of lacosamide has not been completely characterised. The major compounds excreted in urine are unchanged lacosamide (approximately 40% of the dose) and its O-desmethyl metabolite less than 30%. A polar fraction proposed to be serine derivatives accounted for

approximately 20% 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 found in the urine.

CYP2C19, 2C9 and 3A4 are mainly responsible for the formation of the O-desmethyl metabolite. 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). No other enzymes have been identified to be involved in the metabolism of lacosamide.

The plasma concentration of O-desmethyl-lacosamide is approximately 15% of the concentration of lacosamide in plasma. This major metabolite has no known pharmacological activity.

Elimination

Lacosamide is primarily eliminated from the systemic circulation by renal excretion and biotransformation. After oral and intravenous administration of radiolabeled lacosamide, approximately 95% of radioactivity administered was recovered in the urine and less than 0.5% in the faeces. The elimination half-life of the unchanged drug is approximately 13 hours. The pharmacokinetics is dose-proportional and constant over time, 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.

Pharmacokinetics in special patient groups

Gender

Clinical trials indicate that gender does not have a clinically significant influence on the plasma concentrations of lacosamide.

Race

There are no clinically relevant differences in the pharmacokinetics of lacosamide between Asian, Black, and Caucasian subjects.

Renal impairment

The AUC of lacosamide was increased by approximately 30% in mildly and moderately and 60% in severely renal impaired patients and patients with endstage renal disease requiring haemodialysis compared to healthy subjects, whereas C_{max} was unaffected.

Lacosamide is effectively removed from plasma by haemodialysis. Following a 4-hour haemodialysis treatment, AUC of lacosamide is reduced by approximately 50%. Therefore dosage supplementation following haemodialysis is recommended (see Dosage and Administration). The exposure of the O-desmethyl metabolite was several-fold increased in patients with moderate and severe renal impairment. In absence of haemodialysis in patients with endstage renal disease, the levels were increased and continuously rising during the 24-hour sampling. It is unknown whether the increased metabolite exposure in endstage renal disease subjects could give rise to adverse effects but no pharmacological activity of the metabolite has been identified.

Hepatic impairment

Subjects with moderate hepatic impairment (Child-Pugh B) showed higher plasma concentrations of lacosamide (approximately 50% higher AUC_{norm}). The higher exposure was partly due to a reduced renal function in the studied subjects. The decrease in non-renal

clearance in the patients of the study was estimated to give a 20% increase in the AUC of lacosamide. The pharmacokinetics of lacosamide has not been evaluated in severe hepatic impairment (see Dosage and Administration).

Elderly (over 65 years of age)

In a study in elderly men and women including 4 patients >75 years of age, 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.

A general dose reduction is not considered to be necessary unless indicated due to reduced renal function (see Dosage and Administration).

CYP2C19 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.

Preclinical safety data

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

In the repeated dose toxicity studies, mild reversible liver changes were observed in rats starting at about 3 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.

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 systemic exposure levels similar to the expected clinical exposure. Since higher exposure levels could not be tested in animals due to maternal toxicity, data are insufficient to fully characterise the embryofetotoxic and teratogenic potential of lacosamide.

Studies in 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 can not 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 0.5 times that in humans at the MRHD.

CLINICAL TRIALS

The efficacy of Vimpat as add-on therapy in partial-onset seizures was established in three 12-week, randomized, double-blind, placebo-controlled, multicenter trials in adult patients. Patients enrolled 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. 84% of patients were taking 2 to 3 concomitant AEDs with or without concurrent vagal nerve stimulation.

Trial E1 compared doses of Vimpat 200 mg, 400 mg, and 600 mg/day with placebo. Trial E2 compared doses of Vimpat 400 mg and 600 mg/day with placebo. Trial E3 compared doses of Vimpat 200 mg and 400 mg/day with placebo. The trials required forced up-titration to the target (randomized) dose over up to 6 weeks (Trial E1 and Trial E2) or 4 weeks (Trial E3). In all 3 trials, active treatment was initiated at 100 mg/day (50 mg given twice daily) and increased in weekly increments of 100 mg/day to the target dose. Subjects randomized to Vimpat 600 mg/day in Trial E1, Vimpat 400 mg and 600 mg/day in Trial E2, and Vimpat 400 mg/day in Trial E3 received active drug beginning at Week 1. To facilitate trial blinding, subjects randomized to Vimpat 200 mg and 400 mg/day in Trial E1 received placebo for the first 4 or 2 weeks, respectively, and subjects randomized to Vimpat 200 mg/day in Trial E3 received placebo for the first 2 weeks.

In all three trials, following an 8-week Baseline Phase to establish Baseline seizure frequency prior to randomization, subjects were randomized and titrated to the randomized 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). Treatment was maintained for 12 weeks.

A reduction over placebo in seizure frequency per 28 days, the primary variable in all three trials, was significant with Vimpat treatment at doses of 200 mg (Trial E3), 400 mg (Trials E1, E2, and E3), and 600 mg/day (Trials E1 and E2). (Table 1, Figure 1). The 50% responder rates for 400 mg and 600 mg/day Vimpat were also statistically superior to placebo. (Figure 2)

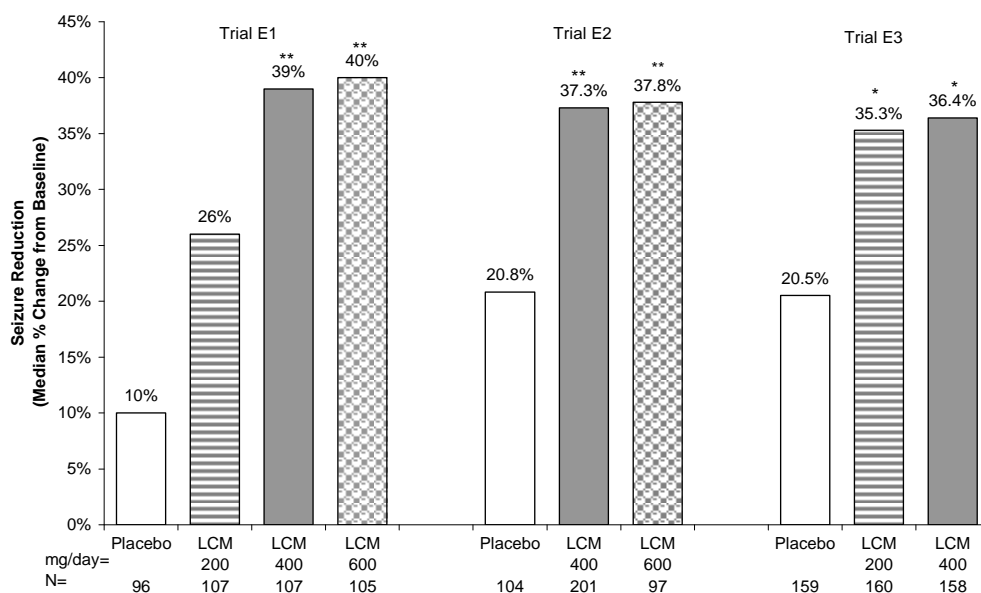
Among the subjects who completed the 12-week Maintenance Phase, a total across all three trials 751 of 12 (3.3%) and 6 (4.8%) subjects taking Vimpat 400 mg and 600 mg/day, respectively, were seizure-free compared with 3 (0.9%) subjects taking placebo.

Table 1 – Vimpat Reduction in Partial Seizure Frequency per 28 Days from Baseline to the Maintenance Phase

Randomized Treatment Group	Number of Patients per Treatment Group	Median Baseline Seizure Frequency per 28 Days	Median Percent Reduction from Baseline	Percent Reduction Over Placebo
Trial E1				
Placebo	96	11	10%	N/A
200 mg/day	107	13	26%	14.6%
400 mg/day	107	13	39%	28.4%**
600 mg/day	105	11	40%	21.3%**
Trial E2				
Placebo	104	15	20.8%	N/A
400 mg/day	201	12	37.3%	21.6%**
600 mg/day	97	17	37.8%	24.6%**
Trial E3				
Placebo	159	10	20.5%	N/A
200 mg/day	160	12	35.3%	14.4%*
400 mg/day	158	10	36.4%	15.0%*

*Significant at the 0.0500 level; **Significant at the 0.0100 level; Percent reduction over placebo and corresponding p-values are based on log-transformed data from pairwise treatment ANCOVA models. Note: Maintenance Phase includes data for the Titration Phase for patients who discontinued prior to entering the Maintenance Phase.

Figure 1 – Median Percent Reduction in Seizure Frequency per 28 days from Baseline to the Maintenance Phase by Dose

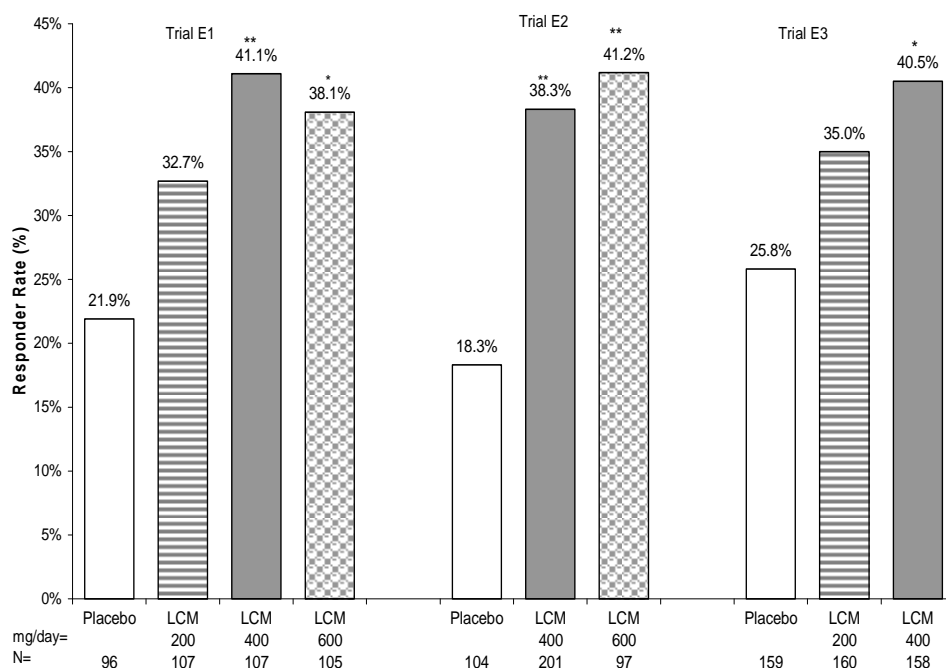


LCM = lacosamide

*Significant at the 0.0500 level; **Significant at the 0.0100 level

p-values are based on log-transformed data from pairwise treatment ANCOVA models

Figure 2 – Responder Rate ($\geq 50\%$ reduction in seizure frequency)



LCM = lacosamide

*Significant at the 0.0500 level; **Significant at the 0.0100 level
p-values are based on pairwise treatment logistic regression models

Note: Responder rate is the proportion of patients with $\geq 50\%$ reduction in seizure frequency per 28 days from Baseline to the Maintenance Phase

INDICATIONS

Vimpat (lacosamide) tablets are indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older.

Vimpat (lacosamide) injection is an alternative for patients when oral administration is temporarily not feasible.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

Known second- or third-degree antroventricular (AV) block.

PRECAUTIONS

Dizziness

Treatment with lacosamide has been associated with dizziness which could increase the occurrence of accidental injury or falls. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication (see Adverse Effects).

Cardiac rhythm and conduction

Prolongations in PR interval with lacosamide have been observed in clinical studies.

Lacosamide should be used with caution in patients with known conduction problems or severe cardiac disease such as a history of myocardial infarction or heart failure. Caution should especially be exerted when treating elderly patients as they may be at increased risk of cardiac disorders or when lacosamide is used in combination with products known to be associated with PR prolongation.

Second degree or higher AV block has been reported in post-marketing experience. In the placebo-controlled trials of lacosamide in epilepsy patients, atrial fibrillation or flutter were not reported; however both have been reported in open-label epilepsy trials and in post-marketing experience (see Adverse Effects – Post-marketing experience).

Patients should be made aware of the symptoms of second-degree or higher AV block (e.g. slow or irregular pulse, feeling of lightheaded and fainting) and of the symptoms of atrial fibrillation and flutter (e.g. palpitations, rapid or irregular pulse, shortness of breath). Patients should be counselled to seek medical advice should any of these symptoms occur.

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for lacosamide. Therefore patients should be monitored for signs of suicidal ideation and behaviours 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.

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

No data on the interaction of lacosamide with alcohol are available.

Effects on fertility

There are no human data on the effects of lacosamide on male or female 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 MRHD.

Use in pregnancy (Category B3)

Risk related to epilepsy and antiepileptic medicinal products in general: For all anti-epileptic drugs, it has been shown that in the offspring of women treated with epilepsy, the prevalence of malformations is two to three times greater than the rate of approximately 3% in the general population. In the treated population, an increase in malformations has been noted with polytherapy, however, the extent to which the treatment and/or the illness is responsible has not been elucidated. Moreover, effective antiepileptic therapy must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the foetus.

The risk of having an abnormal child as a result of antiepileptic medication is far outweighed by the dangers to the mother and foetus of uncontrolled epilepsy.

It is recommended that:

- women on antiepileptic drugs (AEDs) receive prepregnancy counselling with regard to the risk of fetal abnormalities;
- AEDs should be continued during pregnancy and monotherapy should be used if possible at the lowest effective dose as risk of abnormality is greater in women taking combined medication;
- folic acid supplementation (5mg) should be commenced four weeks prior to and continue for twelve weeks after conception;
- specialist prenatal diagnosis including detailed mid-trimester ultrasound should be offered.

There are no adequate data from the use of lacosamide in pregnant women. Studies in animals did not indicate any teratogenic effects in rats or rabbits, but embryotoxicity was observed in rats and rabbits at maternal toxic doses (see Precautions - Effects on fertility). The potential risk for humans is unknown.

Lacosamide should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus). If women decide to become pregnant, the use of this product should be carefully re-evaluated.

Use in lactation

It is unknown whether lacosamide is excreted in human breast milk. Animal studies have shown excretion of lacosamide in breast milk. Because many drugs are excreted into human milk, a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Vimpat should be made taking into account the benefit of breast-feeding to the child and the benefit of Vimpat therapy to the woman.

Use in children

Vimpat is not recommended for use in children under 16 years of age.

Use in the elderly

The experience with lacosamide in elderly patients with epilepsy is limited. Age associated decreased renal clearance with an increase in AUC levels should be considered in elderly patients (see Pharmacology – Pharmacokinetic properties – Renal impairment).

Carcinogenicity

Carcinogenicity studies with lacosamide in mice and rats did not reveal any evidence of drug-related carcinogenicity in either species. Mice and rats received lacosamide once daily by oral administration for 104 weeks at doses producing plasma exposures (AUC) up to approximately 1 and 3 times, respectively, the plasma AUC in humans at the maximum recommended human dose (MRHD) of 400 mg/day.

Genotoxicity

Lacosamide did not induce gene mutations in the Ames test, but at high concentrations induced an equivocal response without, and a weak positive response with metabolic activation in the in vitro mouse lymphoma assay. No effects were observed in vivo in the

mouse micronucleus test or the rat unscheduled DNA synthesis (UDS) test. Therefore, the relevance of the single positive in vitro mutagenicity test is not known.

Cardiac toxicity

A safety pharmacology study with intravenous administration of lacosamide in anesthetized dogs showed transient increases in PR interval and QRS complex duration and decreases in blood pressure most likely due to a cardiodepressant action. These transient changes started in the same concentration range as after maximum recommended clinical dosing. In anesthetized dogs and Cynomolgus monkeys, at intravenous doses of 15-60 mg/kg, slowing of atrial and ventricular conductivity, atrioventricular block and atrioventricular dissociation were seen.

Interactions with other medicines

Lacosamide should be used with caution in patients treated with medicinal products known to be associated with PR prolongation (e.g. carbamazepine, lamotrigine, pregabalin) and in patients treated with class I antiarrhythmic drugs. However, subgroup analysis did not identify an increased magnitude of PR prolongation in patients with concomitant administration of carbamazepine or lamotrigine in clinical trials.

In vitro data

Data generally suggest that lacosamide has a low interaction potential. *In vitro* studies indicate that lacosamide does not induce the enzyme activity of drug metabolising cytochrome P450 isoforms CYP1A2, 2B6, 2C9, 2C19 and 3A4. Lacosamide did not inhibit CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1, 3A4/5 at plasma concentrations observed in clinical trials. *In vitro* data suggest that lacosamide has the potential to inhibit CYP2C19 at therapeutic concentrations. Lacosamide was not a substrate or inhibitor for P-glycoprotein.

In vivo data

Clinical data indicate that lacosamide does not inhibit or induce the enzyme CYP2C19 and 3A4. Furthermore an interaction study with omeprazole (CYP2C19-inhibitor) demonstrated no clinically relevant changes in lacosamide plasma concentrations and no inhibitory effects on omeprazole pharmacokinetics.

Strong enzyme inducers such as rifampicin or St John's wort (*Hypericum perforatum*) may moderately reduce the systemic exposure of lacosamide. Therefore, starting or ending treatment with these enzyme inducers should be done with caution.

Antiepileptic drugs

In interaction trials lacosamide (400 mg/day) did not significantly affect the plasma concentrations of carbamazepine (400 mg/day) and valproic acid (600 mg/day). Lacosamide plasma concentrations were not affected by carbamazepine and by valproic acid.

The placebo-controlled 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 lacosamide at any dose.

A population PK analysis estimated that concomitant treatment with other anti-epileptic drugs known to be enzyme inducers (carbamazepine, phenytoin, phenobarbital, in various doses) decreased the overall systemic exposure of lacosamide by 25%.

Oral contraceptives

In an interaction trial 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.

Others

Interaction trials showed that lacosamide (400 mg/day) had no effect on the pharmacokinetics of digoxin (0.5 mg once daily).

There was no clinically relevant interaction between lacosamide (400 mg/day) and metformin (500 mg three times a day).

Omeprazole (40 mg once daily) increased the AUC of lacosamide by 19% (300 mg, single dose) and thus within accepted bioequivalence range. Therefore, the effect is considered as of no clinical relevance. Lacosamide (600 mg/day) did not affect the single-dose pharmacokinetics of omeprazole (40 mg).

Protein binding

Lacosamide has a low protein binding of less than 15%. Therefore, clinically relevant interactions with other drugs through competition for protein binding sites are considered unlikely.

Effect on ability to drive or operate machinery

Vimpat may have minor to moderate influence on the ability to drive and use machines. Lacosamide treatment has been associated with dizziness or blurred vision. Accordingly, patients should be advised not to drive a car or to operate other potentially hazardous machinery until they are familiar with the effects of Vimpat on their ability to perform such activities.

ADVERSE EFFECTS

Based on the analysis of pooled placebo-controlled clinical trials in 1,308 patients with partial-onset seizures, a total of 61.9% of patients randomized to lacosamide and 35.2% of patients randomized to placebo reported at least 1 adverse reaction. The most frequently reported adverse reactions with lacosamide treatment were dizziness, headache, nausea and diplopia. They were usually mild to moderate in intensity. Some were dose-related and could be alleviated by reducing the dose. Incidence and severity of CNS and gastrointestinal (GI) adverse reactions usually decreased over time. Overall in controlled studies the discontinuation rate due to adverse reactions was 12.2% for patients randomized to lacosamide and 1.6% for patients randomized to placebo. The most common adverse reaction resulting in discontinuation of lacosamide therapy was dizziness.

The table below shows the frequencies of adverse reactions by system organ class which have been reported in pooled placebo-controlled clinical trials with an incidence rate of $\geq 1\%$ in the lacosamide group and which are $>1\%$ more than placebo. The frequencies are defined as

follows: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2 - Incidence of Adverse Reactions during the Treatment Phase

System organ class	Very common	Common
Psychiatric disorders		Depression
Nervous system disorders	Dizziness Headache	Balance disorder Coordination abnormal Memory impairment Cognitive disorder Somnolence Tremor Nystagmus
Eye disorders	Diplopia	Vision blurred
Ear and labyrinth disorders		Vertigo
Gastrointestinal disorders	Nausea	Vomiting Constipation Flatulence
Skin and subcutaneous tissue disorders		Pruritus
General disorders and administration site conditions		Gait disturbance Asthenia Fatigue
Injury, poisoning and procedural complications		Fall Skin laceration

The use of lacosamide is associated with dose-related increase in the PR interval. Adverse reactions associated with PR interval prolongation (e.g. atrioventricular block, syncope, bradycardia) may occur. In epilepsy patients the incidence rate of reported first degree AV Block is uncommon, 0.7%, 0%, 0.5% and 0% for lacosamide 200 mg, 400 mg, 600 mg or placebo, respectively. No second or higher degree AV Block was seen in lacosamide treated epilepsy patients. In patients with diabetic neuropathic pain, second degree AV Block has been rarely reported ($< 0.1\%$).

The incidence rate for syncope is uncommon and did not differ between lacosamide treated epilepsy patients (0.1%) and placebo treated epilepsy patients (0.3%). In the short-term controlled trials in patients with diabetic neuropathy, 1.2% of patients who were treated with lacosamide reported an adverse reaction of syncope or loss of consciousness, compared to 0% of placebo-treated patients with diabetic neuropathy.

In the short-term investigational trials of lacosamide in epilepsy patients, there were no cases of atrial fibrillation or flutter, however both have been reported in open-label epilepsy trials. In patients with diabetic neuropathy, 0.5% of patients treated with lacosamide experienced an adverse reaction of atrial fibrillation or atrial flutter, compared to 0% of placebo-treated patients.

Abnormalities in liver function tests have been observed in controlled trials with lacosamide in adult patients with partial-onset seizures who were taking 1 to 3 concomitant anti-epileptic drugs. Elevations of ALT to $\geq 3x$ ULN occurred in 0.7% (7/935) of lacosamide patients and 0% (0/356) of placebo patients.

In addition, the following potentially important adverse drug reactions have been identified as being reported in pooled clinical trials with an incidence rate not meeting the criteria used above:

- Psychiatric disorders
Common: confusional state
- Nervous system disorders
Common: hypoesthesia, dysarthria, disturbance in attention
- Ear and labyrinth disorders
Common: tinnitus
- Gastrointestinal disorders
Common: dyspepsia, dry mouth
- General disorders and administration site conditions
Common: irritability
- Musculoskeletal and connective tissue disorders
Common: muscle spasms

Intravenous administration

Adverse reactions with intravenous administration generally appeared similar to those observed with the oral formulation, although intravenous administration was associated with local adverse events such as injection site pain or discomfort (2.5%), irritation (1%), and erythema (0.5%).

Post-marketing experience

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported in post-marketing experience. Data are insufficient to support an estimate of their incidence in the population to be treated.

- Immune system disorders
Drug hypersensitivity reactions

Multiorgan hypersensitivity reactions have been reported in patients with some antiepileptic agents. These reactions are variable in expression but typically present with fever and rash and can be associated with involvement of different organ systems. Potential cases have been reported rarely with lacosamide and if multiorgan hypersensitivity reaction is suspected, Vimpat should be discontinued.
- Psychiatric disorders
Euphoric mood, suicide attempt and suicidal ideation, aggression, agitation, psychotic disorder, insomnia, hallucination
- Cardiac disorders
Bradycardia, atrioventricular block, atrial fibrillation and atrial flutter

- Hepatobiliary disorders
Liver function test abnormal
- Skin and subcutaneous tissue disorders
Rash, angioedema, urticaria

DOSAGE AND ADMINISTRATION

Vimpat must be taken twice a day. The recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after one week.

Depending on 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). Vimpat may be taken with or without food.

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).

Vimpat therapy can be initiated with either oral or IV administration. 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.

The solution for injection is infused over a period of 15 to 60 minutes twice daily. There is experience with twice daily infusions of Vimpat up to 5 days.

Use in patients with impaired renal function

No dose adjustment is necessary in mildly and moderately renally impaired patients ($CL_{CR} > 30$ mL/min). A maximum dose of 250 mg/day is recommended for patients with severe renal impairment ($CL_{CR} \leq 30$ mL/min) and in patients with endstage renal disease. For patients requiring haemodialysis a supplement of up to 50% of the divided daily dose directly after the end of haemodialysis is recommended. Treatment of patients with end-stage renal disease should be made with caution as there is little clinical experience and accumulation of a metabolite (with no known pharmacological activity). In all patients with renal impairment, the dose titration should be performed with caution (see Pharmacology – Pharmacokinetics in special patient groups).

Use in patients with impaired hepatic function

No dose adjustment is needed for patients with mild to moderate hepatic impairment. The dose titration in these patients should be performed with caution considering co-existing renal impairment. The pharmacokinetics of lacosamide has not been evaluated in severely hepatic impaired patients (see Pharmacology – Pharmacokinetics in special patient groups).

Use in elderly (65 years and older)

No dose reduction is necessary in elderly patients. The experience with lacosamide in elderly patients with epilepsy is limited. Age-associated decreased renal clearance should be considered in elderly patients (see 'Use in patients with impaired renal impairment' above and Pharmacology – Pharmacokinetics in special patient groups).

Use in children

Vimpat is not recommended for use in children under 16 years of age as there is no data on safety and efficacy in these age groups.

OVERDOSAGE

Symptoms

There is limited clinical experience with lacosamide overdose in humans. Clinical symptoms (dizziness and nausea) following doses of 1200 mg/day were mainly related to the central nervous and gastrointestinal system and resolved with dose adjustments.

The highest reported overdose in the clinical development program for lacosamide was 12 g taken in conjunction with toxic doses of multiple other antiepileptic drugs. The subject was initially comatose and then fully recovered without permanent sequelae.

Management of overdose

There is no specific antidote for overdose with lacosamide. Treatment of lacosamide overdose should include general supportive measures and may include haemodialysis if necessary (see Pharmacology – Pharmacokinetic properties).

PRESENTATION AND STORAGE CONDITIONS

Film-coated tablets

Vimpat film-coated tablets are blister packed and available in strengths of 50 mg, 100 mg, 150 mg and 200 mg lacosamide. Do not halve tablets. Dose equivalence when the tablets are divided has not been established.

50 mg: Pinkish, oval debossed with 'SP' on one side and '50' on the other side. Available in blister packs containing 14, 56* and 168* tablets.

100 mg: Dark yellow, oval debossed with 'SP' on one side and '100' on the other side. Available in blister packs containing 14, 56 and 168* tablets.

150 mg: Salmon, oval debossed with 'SP' on one side and '150' on the other side. Available in blister packs containing 14, 56 and 168* tablets.

200 mg: Blue, oval debossed with 'SP' on one side and '200' on the other side. Available in blister packs containing 14*, 56 and 168* tablets.

*not available in New Zealand

Store Vimpat film-coated tablets below 25°C.

Injection

Vimpat (lacosamide) 200 mg/20mL injection is supplied in 20 mL colourless glass vials with a rubber closure packaged in a carton containing 1 vial* and 5 vials. The solution for injection is single use only. Any unused solution should be discarded.

*not available in New Zealand

Store Vimpat injection below 25°C.

Vimpat injection can be administered intravenously without further dilution or may be diluted before use. The product solution was found to be physically compatible and chemically stable for at least 24 hours when mixed with the following diluents and stored in glass or PVC bags at ambient temperature:

Sodium chloride 0.9% solution

Dextrose 5% solution

Lactated Ringer's solution

To reduce microbiological hazard, use as soon as practicable after preparation. If storage is necessary, hold at 2-8°C for not more than 24 hours.

Product with particulate matter or discolouration should not be used.

MEDICINE CLASSIFICATION

Prescription Medicine

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