

Lacosamide for the treatment of partial-onset seizures

Lacosamide is a recently approved antiepileptic drug for the adjunctive treatment of partial-onset seizures in adults. It is a functionalized amino acid with a novel mechanism of action, possesses excellent oral absorption, has negligible protein binding, interacts minimally with other antiepileptic drugs and is excreted mainly in the urine. It is efficacious at significantly reducing the frequency of partial-onset seizures by approximately 36–39% at doses of 400 mg/day, compared with just 10–20% reduction for placebo. It is generally well tolerated, with its main dose-related side effect being dizziness. It has no known end-organ toxicities, although it can increase the PR interval. It is likely to be an important contribution to the treatment of individuals with refractory partial-onset seizures.

KEYWORDS: epilepsy ■ lacosamide ■ partial seizures ■ pharmacology

Overview of the market

Epilepsy is defined as a chronic condition characterized by recurrent epileptic seizures [1]. It is one of the most common neurological conditions, with at least 50 million people afflicted worldwide [2]. Epileptic seizures are defined as changes in behavior or perception brought about by excessive activity of neurons in the brain [1]. Epileptic seizures can be either partial or generalized in onset. Partial-onset seizures, sometimes referred to as focal-onset seizures, initially arise from one part of the brain, while generalized seizures are simultaneously recorded across the whole scalp. The majority of individuals with epilepsy suffer from partial-onset epileptic seizures.

Antiepileptic drugs (AEDs) are the mainstay of the modern treatment of epilepsy. The goal of treatment is to decrease the frequency and intensity of epileptic seizures in order to ultimately achieve complete seizure control. In the USA, the most frequently prescribed AED is phenytoin followed by levetiracetam. However, despite AED treatment 20–40% of individuals with epilepsy continue to suffer from epileptic seizures [3]. Obviously, there is an opportunity for new AEDs to make an impact on epilepsy care.

Introduction to lacosamide

Lacosamide (Vimpat®) is a functionalized amino acid that has antiseizure properties. It has simple pharmacokinetics, low potential for drug–drug interactions and is usually well tolerated with no known significant end-organ toxicities. It

was effective in animal models of epilepsy and in Phase III randomized, placebo-controlled, double-blinded trials in patients with partial-onset seizures. It is currently under investigation for other types of seizures and circumstances. It has gained popularity owing to its novel mechanism of action, relatively low toxicity, substantial efficacy and its availability as a tablet, in oral solution and intravenous formulations.

Chemistry

The chemical name of lacosamide is (R)-2-acetamido-*N*-benzyl-3-methoxypropionamide and its chemical formula is $C_{13}H_{18}N_2O_3$. It is a white to light-yellow crystalline powder with a molecular weight of 250.3 Da [4]. The structural formula is shown in FIGURE 1.

History of lacosamide

In 1985, Cortes *et al.* reported that a simple amino acid derivative, *N*-acetyl-D,L-alanine benzylamide was effective in preventing seizures in animal models of epilepsy [5]. This compound was derived through the process of ‘functionalization’, in which new compounds are synthesized through the addition of various functional groups. Multiple subsequent studies by Kohn *et al.* confirmed the anticonvulsant properties of these functionalized amino acids [6–10]. After systematic evaluation of over 100 derivatives of the compound synthesized, Choi *et al.* synthesized the derivative (R)-2-acetamido-*N*-benzyl-3-methoxypropionamide in 1996, and demonstrated its superior efficacy in preventing seizures in animal models of epilepsy [11].

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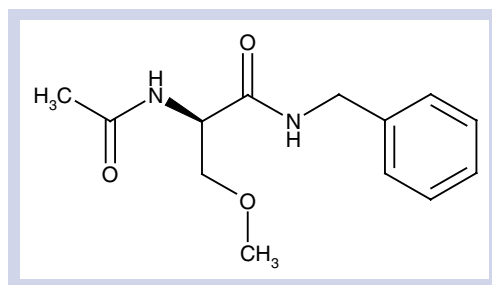


Figure 1. Lacosamide.

Lacosamide was termed ADD 234034 in the NIH AED development program but was called harkoseride during the first studies conducted in humans. Harris Federal Research Consultants recognized the drug's potential and were responsible for its development. An initial Phase II proof-of-principle study in 13 epilepsy patients suggested it was well tolerated and demonstrated some efficacy. It was then licensed to Schwarz Pharma, who named it SPM927. Schwarz designed and carried out the clinical development program and it was finally given the official name of lacosamide and marketed under the brand name of Vimpat by UCB Pharma.

Lacosamide was evaluated and demonstrated to be effective in multiple animal models of epilepsy before it was approved for clinical studies in humans. These models included the maximal electroshock test, the 6 Hz psychomotor seizure test and the kindling model. In the maximal electroshock test, which is regarded as a test of a compound's ability to inhibit seizure spread in generalized tonic-clonic seizures [12] as well as its ability to protect against partial seizures [13], it protected both mice at an effective dose for 50% of animals (ED_{50}) = 4.5 mg/kg intraperitoneally, and rats at ED_{50} = 3.9 mg/kg orally. In the 6 Hz model, which is considered a model for treatment-resistant seizures [12], lacosamide demonstrated efficacy at ED_{50} = 9.99 mg/kg [14]. Finally, in the kindling model, which is thought to be a model of complex partial seizures, the calculated ED_{50} for a reduction in seizure score from five to three or less in fully kindled rats was 13.5 mg/kg [4]. In other words, the average seizure induced by an electrical stimulus was reduced from a full convulsion to just forelimb clonus.

However, lacosamide was not effective in all animal models of epilepsy. Lacosamide proved ineffective at inhibiting seizure activity induced by subcutaneous injection of the chemoconvulsant pentylenetetrazole, which is considered a model of absence seizures. It was

also inactive against clonic seizures induced by infusion of the γ -aminobutyric acid receptor antagonist, bicuculline, and the chloride-channel blocker, picrotoxin [14]. Despite its ineffectiveness in these chemoconvulsant animal models of seizures, it was considered a good candidate for adjunctive therapy of partial seizures in humans because of its effectiveness in other previously discussed models.

Pharmacodynamics

Lacosamide's antiseizure properties are thought to arise from its unique ability to enhance the slow inactivation of sodium channels [15]. This is in contrast to phenytoin and carbamazepine, which work primarily through prolonging the refractory period of fast sodium channels [16]. In addition, lacosamide has been identified as a binding partner to collapsing-response mediator protein-2, which may also act to enhance slow inactivation of sodium channels and could have other cellular effects on differentiation, polarization and axonal outgrowth [4,17–19].

Pharmacokinetics & metabolism

Lacosamide is rapidly and almost completely absorbed from the GI tract and has a high oral bioavailability of approximately 100% with negligible first-pass metabolism [17,18]. Food does not appear to affect its absorption and peak plasma concentration occurs 0.5–4.0 h post dose [19]. Bioequivalence of the oral solution and the tablet form has been established [101]. Oral bioavailability has also been demonstrated to be comparable to the intravenous formulation [20]. The volume of distribution of lacosamide is 0.6 l/kg [102]. Protein binding is considered inconsequential with less than 15% of the drug bound to plasma proteins [18]. The metabolism of lacosamide has not been completely characterized [21]. It is known that its terminal half-life is approximately 13 h, allowing for convenient twice-daily treatment. Steady-state serum levels are reached in 2–3 days [22].

The cytochrome (CYP) P450 system participates in the metabolism of lacosamide mainly through the formation of the inactive *O*-desmethyl metabolite by the isoenzyme CYP2C19 [17,23]. However, the pharmacokinetics of lacosamide were not significantly different when administered to humans who were CYP2C19 extensive or poor metabolizers [24]. Furthermore, when the known 2C19 inhibitor, omeprazole, was administered concomitantly it did not alter the pharmacokinetics of lacosamide [24].

Other possible drug interactions with lacosamide have been investigated. It has been demonstrated that lacosamide does not affect carbamazepine pharmacokinetics and *vice versa* [21]. Phase I trials also demonstrated that lacosamide does not interact with valproic acid [25]. Lacosamide does not appear to affect the pharmacokinetics of digoxin, metformin, levonorgestrel or ethinylestradiol [102]. In clinical trials that were conducted to demonstrate efficacy, lacosamide administration did not have significant effects on the plasma concentrations of carbamazepine, active carbamazepine metabolites, lamotrigine, phenytoin, topiramate or valproic acid [26–28]. In one trial, it did appear to decrease the plasma concentration of the monohydroxy derivative of oxcarbazepine, which is an active metabolite [28].

Elimination of lacosamide from the systemic circulation is primarily via urinary excretion and biotransformation. A total of 40% of the drug is excreted unchanged, 30% as the *O*-desmethyl metabolite and 20% as a polar fraction with 0.5–2.0% as other metabolites [23]. The total body clearance of lacosamide is 2 l/h [29].

Clinical efficacy

As mentioned previously, multiple Phase I and IIa studies have been completed to characterize lacosamide's tolerability, bioequivalence, pharmacokinetics, pharmacodynamics and potential for drug interactions. Unfortunately, most of these studies are unpublished. However, three randomized, double-blind, placebo-controlled trials have been completed, assessing the efficacy of lacosamide for the adjunctive

treatment of partial seizures (TABLE 1) [26–28]. All the studies used an intention-to-treat analysis with the primary end points of percentage reduction of seizure rate per 28 days, as well as the 50% responder rate, which is the percentage of patients who had a reduction of their seizure frequency by at least 50%. All three studies had an 8-week baseline period, a 4- or 6-week titration period and a 12-week maintenance period. In the 8-week baseline period patients were monitored for eligibility and baseline seizure frequency was determined – they had to have four partial-onset seizures per 28 days, with no longer than 21 days between seizures to be eligible. Once eligibility was determined and an individual was enrolled, they were randomized to the different treatment groups. After the titration period, they were monitored for 12 weeks in the maintenance phase to determine their new seizure frequency for comparison to the baseline frequency in the efficacy analysis.

The first study by Ben-Menachem *et al.* allowed a patient to be on one or two AEDs as well as have a vagus-nerve stimulator [27]. The second study by Halász *et al.* [28] and the third by Chung *et al.* [26] allowed a patient to be on one to three AEDs and a vagus-nerve stimulator.

All three studies demonstrated a significant improvement in both seizure frequency as well as the 50% responder rate at doses of 400 mg/day. Only one of the two studies that tested a 200-mg dose found a difference in outcomes for that dose from placebo, and this was only in the seizure frequency rate. In the two studies that tested a dose of 600 mg/day there was a significant improvement when

Table 1. Lacosamide efficacy trials.

Study	n	Lacosamide dose (mg/day)	Median reduction in seizure frequency (%)	Significance of median reduction from placebo (p-value)	50% responder rate (%)	Significance of 50% responder rate from placebo (p-value)	Ref.
Ben-Menachem <i>et al.</i>	418	200 (n = 107)	26	0.1010	32.70	0.0899	[27]
		400 (n = 108)	39	0.0023 [†]	41.10	0.0038 [†]	
		600 (n = 106)	40	0.0084 [†]	38.10	0.0141 [†]	
		Placebo (n = 97)	10	NA	21.90	NA	
Halász <i>et al.</i>	485	200 (n = 163)	35	0.02 [†]	35.00	0.07	[28]
		400 (n = 159)	36	0.03 [†]	40.50	0.01 [†]	
		Placebo (n = 163)	20.50	NA	25.80	NA	
Chung <i>et al.</i>	405	400 (n = 204)	37.30	0.008 [†]	38.30	<0.001 [†]	[26]
		600 (n = 97)	37.80	0.006 [†]	41.20	<0.001 [†]	
		Placebo (n = 104)	20.80	NA	18.30	NA	

[†]Significant difference from placebo.

NA: Not applicable.

compared with placebo in both outcomes, but there was no significant difference in outcomes between the 400- and 600-mg groups. It should be noted that in the Ben-Menachem *et al.* study, 30% of individuals receiving the 600-mg dose discontinued from the trial owing to adverse events when compared with 19% in the 400-mg group. This was similar in the study by Chung *et al.* where 27% of the 600-mg group and 18% of the 400-mg group discontinued owing to adverse events. This higher discontinuation rate in the 600-mg group in both trials likely accounts for why there was no difference in efficacy seen between the 400- and 600-mg groups. Interestingly, in Chung *et al.*, when the number of secondarily generalized tonic-clonic seizures was considered in secondary analysis, they were reduced by 59.4% for the 400-mg/day group and 93% for the 600-mg/day group compared with just 14.3% for placebo. This improved control of secondarily generalized tonic-clonic seizures was also observed in responder rates of 56.0% for the 400-mg/day group and 70.2% in the 600-mg/day group when compared with the placebo responder rate of 33.3%. The detailed outcomes of each study are summarized in TABLE 1.

In summary, three trials have demonstrated the ability of lacosamide to decrease partial-onset seizure frequency at doses of 400 and 600 mg/day. Lacosamide probably has efficacy at reducing seizure frequency at 200 mg/day. While no study has demonstrated that 400 mg/day of lacosamide is better than 600 mg/day in reducing partial seizure frequency based on intention-to-treat analysis, the lack of difference between groups is likely to be caused by the unacceptable side effects of 600 mg/day of lacosamide in some individuals. In those that can tolerate 600 mg/day, there is a likely increased efficacy of the higher dose. In addition, there appears to be better control of secondarily generalized tonic-clonic seizures in those individuals who can tolerate 600 mg/day lacosamide.

Postmarketing surveillance

There is no standardized US FDA requirement for surveillance of lacosamide under the specified risk evaluation and mitigation strategies program. However, similar to other medications in the AED class, lacosamide carries a warning of suicidality. It is suggested in the package insert that patients should be warned of this potential problem and the package insert

contains a patient guide with this information. However, it is rarely discussed in clinical practice because few people are aware of it or because they think it is an unlikely risk for AEDs. Common clinical experience has not identified any problems that were not known from clinical trials [30].

The dosing of lacosamide in clinical practice has been similar to the experience in clinical trials. It was initiated at a dose of 100 mg twice daily in clinical trials and it can also be initiated this way in clinical practice. However, there is typically no hurry when it is added to existing therapy. Many patients do not tolerate adverse effects such as dizziness well. Thus, similar to other AEDs, it is advisable to start at a lower dose and increase it gradually. Starting at 100 mg/day and increasing it each week by 100 mg/day to an initial target dose of 300–400 mg/day is very often well tolerated. A dose of 200 mg/day was only equivocally efficacious in clinical trials and 400 mg/day seems to be the beginning of the range at which adverse events were more common. Therefore, an initial target dose of 300 mg/day is reasonable, although 400 mg/day is more supported by clinical trials. Conversely, lacosamide is available as an intravenous formulation. Initial studies suggest it can be well tolerated when loaded as 300 mg over 15 min and then dosed 150 mg twice daily, but lacosamide is not approved for use in this manner [31].

Safety & tolerability

The most common side effect of lacosamide appears to be dizziness. This occurred in up to 55% of individuals on 600 mg/day in one of the Phase III studies [27]. The incidence of dizziness appears to be dose related. Other common side effects that appeared to be dose related were headache, nausea, fatigue, ataxia, abnormal vision, vomiting, nasopharyngitis, diplopia, tremor and nystagmus [26–28]. Dose-related side effects that led to discontinuation from the three Phase III studies included dizziness, diplopia, vertigo, nausea, vomiting and ataxia. There did not appear to be an effect on body weight with lacosamide administration [28].

Lacosamide appears to affect the cardiovascular system. While it does not prolong the QT/QTc interval or the QRS interval, it does appear to produce a small increase in the mean PR interval. It has also been associated with producing an asymptomatic first-degree atrioventricular block, in a small number

of epilepsy patients in clinical trials (three patients in three trials), but this did not necessitate withdrawal of the medication [26–28]. A similar effect is seen in other antiepileptic medications, such as phenytoin and carbamazepine, which act through sodium channel modulation. Lacosamide has also been associated with atrial fibrillation in studies where it was used for the treatment of painful diabetic neuropathy [32]. Therefore, it is wise to use caution when prescribing lacosamide to individuals with cardiac conduction defects or underlying cardiovascular disease.

The hepatic effects of lacosamide appear to be minimal. While liver enzyme elevations were observed in four patients in the three Phase III trials, none of these were associated with a change in liver function as measured by an increasing bilirubin [26–28]. In two of the four patients, when lacosamide was stopped, normalization of the liver enzymes ensued. Normalization occurred in one patient despite lacosamide being continued. It should be noted that two of the four patients had mild elevations in liver enzymes at baseline. However, it would be advisable to be cautious when prescribing lacosamide in patients with liver failure or markedly elevated liver enzymes, given that the effect of lacosamide on these patients has not been investigated.

There is a widely reported link between the use of AEDs in individuals with epilepsy and increased risk of suicidal behavior and ideation [33]. However, there have been no studies assessing this risk for lacosamide. Therefore, we are not able to comment at this time whether lacosamide increases the risk of suicide in epilepsy patients. However, caution should be used when prescribing these medications in patients with epilepsy, particularly when they have a baseline mood disorder.

Regulatory affairs

The EMA approved oral and intravenous formulations of lacosamide for the adjunctive treatment of partial-onset seizures in patients 16 years and older in August 2008. This was followed by approval by the FDA in October 2008 for the same indication in patients aged 17 years and older. These approvals are for ‘adjunctive’ therapy, which means they can be added to a patient’s pre-existing AED therapy. The next appropriate step is to develop it for children, for primary generalized seizures and as monotherapy, for which studies are ongoing [103].

Conclusion & future perspective

Lacosamide is a recently approved AED for the adjunctive treatment of partial-onset seizures. It is a functionalized amino acid with a novel mechanism of action, possesses excellent oral absorption, has negligible protein binding, interacts minimally with other AEDs and is excreted mainly in the urine. It is efficacious at significantly reducing the frequency of partial-onset seizures at doses of 400 mg/day. It is generally well tolerated, with its main dose-related side effect being dizziness. It can have rare but potentially important cardiac effects, by increasing the PR interval or causing atrial fibrillation. Therefore, it should be used with caution in individuals with cardiac conduction defects or cardiovascular disease. However, given its novel mechanism of action, it shows promise in the treatment of individuals with refractory partial-onset seizures.

Lacosamide is being investigated for a larger variety of indications. The availability of an intravenous formulation makes it attractive for use in the treatment of status epilepticus, although efficacy studies for status epilepticus are difficult. Its utility for conversion to monotherapy for partial-onset seizures as well as its efficacy as an adjunctive treatment for generalized-onset seizures are also under investigation. Encouraged by experimental evidence that lacosamide may have antinociceptive action [34–36], it is being investigated as a treatment for fibromyalgia and neuropathic pain [32,37]. Given lacosamide’s novel mechanism of action and recent animal model evidence that it may have anxiolytic properties, it is also reasonable to speculate that lacosamide may be useful in the treatment of psychiatric diseases [38]. However, this area of investigation has yet to begin in humans.

In conclusion, lacosamide is a promising new therapy for the adjunctive treatment of intractable partial-onset seizures. It remains to be seen whether it is useful in the treatment of neuropathic pain disorders, fibromyalgia or psychiatric disease.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Executive summary

Mechanism of action

- Lacosamide's antiseizure properties are thought to arise from its ability to enhance the slow inactivation of voltage-gated sodium channels.

Pharmacokinetic properties

- Lacosamide has 100% oral bioavailability with negligible first-pass metabolism and its oral absorption is not altered when administered with food.
- Lacosamide is negligibly protein bound.
- Known inhibitors and inducers of the cytochrome P450 system do not appear to alter the pharmacokinetics of lacosamide. Lacosamide does not appear to have clinically significant effects on the concentrations of other common antiepileptic drugs.
- Elimination of lacosamide is primarily through urinary excretion and biotransformation.

Clinical efficacy

- One Phase IIb and three Phase III trials have demonstrated efficacy of lacosamide in reducing the frequency of intractable partial-onset seizures at doses of 200 and 400 mg.
- A dose of 600 mg/day demonstrated no increased group efficacy when compared with doses of 400 mg/day, although it may have additional efficacy against secondary generalized tonic-clonic seizures.

Safety & tolerability

- Lacosamide can increase the PR interval and has occasionally been associated with atrial fibrillation.
- Hepatic toxicity appears to be minimal.
- Caution should be used in patients with a baseline mood disorder as antiepileptic drug administration has been linked to an increased risk of suicidal ideation and behavior.
- Its main dose-related side effect is dizziness.

Drug interactions

- Lacosamide does not appear to have significant interactions with other commonly used antiepileptic drugs.

Dose & administration

- Lacosamide is dosed twice daily and can be given without food or drink restrictions.

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