National Drug Monograph
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Lacosamide (Vimpat®)

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VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary

- Lacosamide is a sodium channel modulator approved as adjunctive therapy in the treatment of partial-onset seizures in epilepsy patients at least 17 years of age. Lacosamide 400mg has demonstrated that it was more effective with responder rates (41.1%, p=0.0038) and median seizure frequency reduction per protocol (39.3%, p<0.0001) and per intention to treat (28.4%, p=0.0023) compared to placebo.
- Both lacosamide 200mg/day and 400mg/day regimens demonstrated similar efficacy, however only the 400mg/day regimen achieved statistical significance in regards to responder rates.
- Lacosamide regimens of 400mg/day and 600mg/day demonstrated statistical significance for both median reduction in seizure frequencies and responder rates. A higher rate of drop-outs due to adverse effects was reported with lacosamide 600mg/day.
- A post hoc analysis of the clinical trials was conducted to assess the response during the lacosamide titration phase and evaluate other antiepileptic drugs (AED) used. The analysis concluded that lacosamide treatment showed a reduction in seizures, regardless of the concomitant AED used.
- Adverse events such as dizziness, nystagmus and convulsion occurred at an overall higher rate in the lacosamide treatment groups.

Introduction[1,2]

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating lacosamide for possible addition to the VA National Formulary; (2) define the role of lacosamide in therapy; and (3) identify parameters for its rational use within the VA system.

Pharmacology/Pharmacokinetics[1-3]

Although the precise mechanism of action for lacosamide is unknown, it has several proposed mechanisms. Preclinical studies have shown that lacosamide is a sodium channel modulator that selectively enhances slow inactivation of the voltage gated sodium channels (VGSC). One proposed mechanism for lacosamide includes stabilizing the hyperexcitable neuronal membranes and inhibiting the neuronal firing. This results in the regulation of the sodium channels and thus reduces the long term availability of the channels. Studies also demonstrate that lacosamide binds to a phosphodiesterase protein called collapsin-response mediator protein-2 (CRMP-2). CRMP-2 controls axonal outgrowth, neuronal differentiation and polarization. Some studies suggest that CRMP-2 expressions in the brain of epileptic patients are dysregulated. It is suggested that the binding between lacosamide and CRMP-2 may block neurotropin-induced axons from growing.

Lacosamide has a rapid absorption and bioavailability of approximately 100%. Lacosamide is less than15% bound to plasma proteins. Steady state plasma concentration with twice daily dosing is attained at approximately 72 hours. Both metabolite and parent drug are excreted in the urine (about 95% of the

drug). Lacosamide is a CYP2C19 substrate however the effects of the other CYP450 enzymes on the drug are unknown. Lacosamide has drug interactions with CYP2C19 inhibitors such as ethinyl estradiol. Caution should be exercised when using lacosamide with other antiepileptic medications such as carbamazepine and phenytoin as they are both CYP2C19 inducers.

Table 1 Pharmacokinetic Characteristic

Parameter	Lacosamide, Oral	Lacosamide, IV
Absorption T_{max}	1 – 4 hours	30-60 min (end of infusion)
Metabolism	Hepatic, CYP2C19	Hepatic, CYP2C19
Bioavailability	100%	100%
Half-life	13 hours	13 hours
Protein Binding	< 15%	< 15%
Excretion	Renal	Renal

FDA Approved Indication(s)[1,2]

Lacosamide is indicated as adjunctive therapy in the treatment of partial onset seizures in patients ≥ 17 years of age with epilepsy.

Potential Off-label Uses[1,2]

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

Potential off-label use includes treatment of diabetic neuropathy and nonconvulsive status epilepticus.

Current VA National Formulary Alternatives[4]

Lacosamide is a sodium channel modulator that selectively enhances slow inactivation of the voltage gated sodium channels. Current VANF alternatives for partial seizures are carbamazepine, lamotrigine, topiramate and levetiracetam. These agents also affect voltage sensitive sodium channels.

For diabetic neuropathy, current VA national formulary alternatives include amitriptyline, desipramine, gabapentin, imipramine, nortriptyline, and venlafaxine.

For nonconvulsive status epilepticus, current VA national formulary alternatives include diazepam, levetiracetam, lorazepam, midazolam, phenobarbital, phenytoin, and propofol.

Dosage and Administration[1,2]

The recommended initial dose of lacosamide is 100 mg/day (divided in 2 doses). Based on clinical response and tolerability, the dose may be increased by 100mg/day in weekly intervals up to the recommended maintenance dose of 200-400 mg/day. In clinical trials, the 600mg/day dose was not shown to be more effective that the 400 mg/day dose and there was a higher rate of adverse events with the higher dose.

Lacosamide is available in oral (tablets and solution) and intravenous (IV) formulations. The oral formulations may be administered with or without food. The total daily dose and frequency of intravenous lacosamide is the same as the oral formulations. Bioavailability of oral lacosamide is comparable to intravenous lacosamide.

IV therapy should only be used temporarily as the long term effects of intravenous lacosamide have not been studied. The IV formulation may be administered without further dilution or may be mixed with compatible diluents (NS, LR, D_5W). Lacosamide should not be admixed with other solutions. If diluted,

it is stable for up to 24 hours when stored in glass or PVC bags at room temperature. Lacosamide IV should be infused over 30-60 minutes. Lacosamide infusions in clinical trials were limited to 5 days.

Special Population

Pregnancy category C:

Lacosamide demonstrated evidence of developmental toxicity in animal models. Potential benefit versus risk should be evaluated when using lacosamide during pregnancy.

Pediatric patients:

Safety and efficacy has not been established in pediatric patients < 17 years old.

Geriatric patients:

Assessment of efficacy in the elderly population is not yet conclusive due to an insufficient number of enrolled patients in controlled clinical trials (n=18). Subgroup analysis of the elderly patients enrolled has demonstrated that AUC and C_{max} of lacosamide in the geriatric patient were approximately 20% higher in comparison to healthy young subjects. This is most likely associated with age related declines in renal function.

Renal impairment (CrCl < 30 mL/min):

The recommended maximum dose is 300 mg/day. Lacosamide is effectively removed from the plasma by hemodialysis and a 50% dose supplementation should be considered after a hemodialysis treatment.

Hepatic impairment (Child-Pugh A & B):

The recommended maximum dose is 300 mg/day. It is not recommended in severe hepatic impairment (Child-Pugh C) since it has not been studied in this population.

Efficacy

Partial Onset Seizures:

Oral efficacy [5-8]

The safety and efficacy of lacosamide as add-on therapy in adults with uncontrolled partial-onset seizures were evaluated in three randomized, double-blind, placebo-controlled trials involving 1,308 patients. Participants were followed over a 12-week maintenance period with the primary efficacy endpoint of seizure frequency reduction. Prior to initiating study medication, participants were enrolled in a baseline, screening period for 8 weeks. During this time, baseline data were collected and patients had to demonstrate poor seizure control as defined by a minimum average of 4 partial onset seizures per 28 days, and no seizure free periods longer than 21 days. Reduction in seizure frequency was quantified by the following:

- Median reduction in seizure frequency per 28 days, or
- Responder rate which is defined as a reduction of at least 50% in patient's seizure frequency compared to baseline period.

Ben-Menachem *et al.*[5]

In a phase II multicenter, double-blind, placebo-controlled trial by Ben-Menachem *et al*., the safety and efficacy of lacosamide as adjunctive therapy in patients established on a maximum of two other AEDs were evaluated. Concomitant AEDs included: carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, topiramate, and valproate. A total of 421 adults with uncontrolled partial-onset seizures were randomized in a 1:1:1:1 ratio to four treatment arms: placebo, lacosamide 200mg/day, 400mg/day, or 600mg/day in two equally divided doses.

At baseline, approximately 84% of patients were taking 2 AEDs and 16% were taking 1 AED. The median seizure frequency per 28 days during the baseline period was between 11-13 seizures. Study

participants who met criteria were then entered into a 6-week dose titration period followed by a 12- week maintenance period. Results were analyzed based on intention-to-treat (ITT).

Table 2 Results to Ben-Menachem *et al.*

	Median % Reduction in Seizure Frequency per 28 days	Median % Reductions in Seizure Frequency over Placebo (ITT)	Median % Reductions in Seizure Frequency over Placebo (Per Protocol)	Responder Rate (ITT)	Responder Rate (Per Protocol)
Placebo	10%			21.9%	21.2%
Lacosamide 200mg/day	26%	14.6% (p=0.1010)	21.5% (p=0.0112)	32.7% (p=0.0899)	38.1% (p=0.0214)
Lacosamide 400mg/day	39%	28.4% (p=0.0023)	39.3% (p<0.0001)	41.1% (p=0.0038)	49.4% (p=0.0002)
Lacosamide 600mg/day	40%	21.3% (p=0.0084)	31.6% (p=0.0002)	38.1% (p=0.0141)	49.2% (p=0.0004)

Of the 418 patients that were randomized, only 75% (312) completed the trial as 17% (73) dropped out due to adverse events. Three patients who completed the trial were excluded after an on-site audit suggested protocol noncompliance. Due to the high drop-out rates, ITT was used to avoid bias associated with the non-random loss of the participants.

After the 12 week maintenance period, lacosamide at doses of 400mg/day and 600mg/day met both the primary endpoints of seizure frequency in the intention-to-treat and the per protocol analyses. As expected, the per protocol data showed more favorable efficacy as it excluded the patients that dropped out due to perceived lack of efficacy and/or adverse effects. It is important to note that responder rates and mean seizure frequency reductions were greater with lacosamide 400mg/day than with lacosamide 600mg/day in both the ITT and per protocol populations. Based on these findings, lacosamide 600mg/day appears to be a poor therapeutic option as it does not have added-efficacy and is associated with an increase in adverse events as compared with 400mg/day.

Related to seizure free periods, lacosamide 400mg/day demonstrated superiority over lacosamide 600mg/day. At baseline, patients reported seizure free periods no longer than 21 days. As a clinically significant marker for improved quality of life, seizure freedom was reported at the completion of the trial. Seizure freedom in this and subsequent trials was defined as no seizures throughout the 12-week maintenance period. In this study, 5 of 107 patients randomized to receive lacosamide 400mg/day achieved seizure freedom. In contrast, only 1 of 106 patients randomized to receive lacosamide 600mg day achieved seizure freedom.

Halasz *et al.* [6]

In a second, similar trial by Halasz *et al.*, 485 patients with uncontrolled partial-onset seizures currently on one to three AEDs were randomized to lacosamide 200mg/day, lacosamide 400mg/day, or placebo in a 1:1:1 ratio. The five most common concomitant AEDs included carbamazepine (47.5%), valproate (32.8%), lamotrigine (30.5%), topiramate (28.2%), and levetiracetam (19.8%). A majority of patients were taking at least 2 to 3 AEDs in addition to their assigned trial medication, 49.9% and 36.9% respectively. Despite combination therapy, the seizure frequency across all treatment groups ranged from 9.9 to 11.5 seizures per 28 days during the 8-week baseline period.

Of the 485 patients who were randomized, only 82.3% (399) completed the trial. About 51% of the drop-outs (44/86) were due to adverse events, more so with the higher dose of lacosamide and most commonly during the titration period. A significantly greater percentage of randomized patients were included in the ITT versus the per protocol group, 98% (477/485) and 82% (399/485) respectively. Of note, two patients

in the lacosamide 200mg group dropped out due to lack of efficacy versus none in the lacosamide 400mg group.

Table 3 Results to *Halasz et al.*

	Median % Reductions in Seizure Frequency Per 28 Days (ITT)	Median % Reductions in Seizure Frequency over Placebo (ITT)	Median % Reductions in Seizure Frequency Per 28 Days (Per Protocol)	Responder Rate (ITT)	Responder Rate (Per Protocol)
Placebo	20.5%		25.4%	25.8%	27.5%
Lacosamide 200mg/day	35.3%	14.4% (p=0.02)	35.3% (p=0.04)	35.0% (p=0.07)	35.0% (p=0.19)
Lacosamide 400mg/day	36.4%	15% (p=0.03)	44.9% (p=0.01)	40.5% (p=0.01)	46.3% (p<0.01)

With regards to percent reduction in seizure frequency, both lacosamide 200mg/day and 400mg/day demonstrated significant reductions over placebo. However, the 400mg/day group did not demonstrate improved efficacy when compared to the 200mg/day group in the ITT population. This result is a contrast to the earlier study by Ben-Menachem *et al*. The mean reduction in seizure frequency with lacosamide 400mg/day was 15% in this trial compared to 28.4% in the Ben-Menachem *et al* trial. This difference in response rates may be partially due to a more difficult to treat population. The Ben-Menachem *et al* study evaluated patients on up to 2 AEDs at baseline while this study evaluated patients taking up to 3 AEDs.

Evaluating responder rates, only the 400mg/day group achieved statistical significance. It is important to note that while lacosamide 200mg/day showed better reduction in seizure frequency in this trial compared to the previous trial by Ben-Menachem *et al*, it still failed to reach statistical significance for responder rate for both ITT and per protocol populations. Failing to reach statistical significance for per protocol analysis is especially relevant since this population is a better marker of true clinical practice. Despite adherence to the study protocol, patients on lacosamide 200mg/day had no benefit in responder rate compared to placebo. While Halasz *et al* concluded that treatment-emergent adverse events (TEAE) were relatively low and were similar between placebo and lacosamide 200mg/day, the reduced efficacy of the lower dosing regimen of lacosamide limits the value of this conclusion.

In this study, seizure freedom was less impressive as there was disparity with the increase in dose. Among those who completed the full maintenance period, 3.5% (5/137) with lacosamide 200mg/day, 2.4% (3/123) with lacosamide 400mg/day, and 2.1% (3/142) with placebo were able to reach this therapeutic goal. Lacosamide 400mg/day showed a 5% increase in percentage of seizure-free days over placebo (p=0.01). However, with only a 5% increase, the clinical significance may be limited.

Chung P. *et al.* [7]

Based on the above two trials, lacosamide 400mg/day was shown to be more efficacious versus lacosamide 200mg/day. In 2010, Chung P. *et al.* conducted a similar trial to assess lacosamide at only the higher dosages. A total of 405 patients were randomized in a 1:2:1 ratio to placebo, lacosamide 400mg/day, or lacosamide 600mg/day. In this study, patients were most commonly taking the following concomitant AEDs: levetiracetam (39.1%), lamotrigine (36.1%), carbamazepine (24.9%), oxcarbazepine (21.4%), phenytoin (18.9%), topiramate (18.2%), valproate (16.9%), and zonisamide (14.7%).

Of the 405 patients that were randomized, 316 (78%) completed the trial with only 280 (69%) included in the per protocol analysis. Of the 89 patients that dropped out, most were documented as due to adverse

events (75%). The higher drop-out rates in this trial are likely due to the use of higher dosages as these have been linked to an increasing rate of adverse events.

Table 4 Results to Chung P. *et al.*

	Median % Reductions in Seizure Frequency Per 28 Days (ITT)	Median % Reductions in Seizure Frequency over Placebo (ITT)	Median % Reductions in Seizure Frequency Per 28 Days (Per Protocol)	Responder Rate (ITT)	Responder Rate (Per Protocol)
Placebo	20.8%		21.7%	18.3%	18.4%
Lacosamide 400mg/day	37.3%	21.6% (p=0.006)	39.6% (p=0.015)	38.3% (p<0.001)	40.0% (p<0.001)
Lacosamide 600mg/day	37.8%	24.6% (p=0.006)	50% (p=0.002)	41.2% (p<0.001)	50.9% (p<0.001)

At the end of the 12-week maintenance period, lacosamide at both 400mg/day and 600mg/day reached statistical significance for both primary efficacy measures of reductions in seizure frequency and responder rate. While both treatment arms were shown to be efficacious in reducing seizure frequency, lacosamide 400mg/day was better tolerated. When looking at a more stringent marker of efficacy, the 75% responder rate for lacosamide 400mg/day and 600mg/day were 20.4% (p=0.005) and 21.6% (p=0.007) respectively, which were both statistically significant when compared to placebo. Again, lacosamide demonstrated efficacy with only marginal benefit associated with the 600mg/day over the 400mg/day regimen.

Based on secondary endpoints, 600mg/day demonstrated better efficacy in achieving complete seizure free days throughout the study as well as improvements in the percentage of seizure-free days. Of the available data, seizure freedom through the maintenance period was demonstrated in 0% (0/95) in the placebo group, 2% (4/201) in lacosamide 400mg/day group, and 5.2% (5/97) in lacosamide 600mg/day group (based on ITT population). Both groups also showed an increase in percentage of seizure-free days over the placebo group. Lacosamide 400mg/day increased seizure free days by 5.3% (p=0.013) and lacosamide 600mg/day by 8.2% (p<0.001). This result parallels the 5% increase in seizure free days achieved with lacosamide 400mg/day in the Halasz *et al* trial.

A total of 16.5% of all patients discontinued lacosamide due to TEAE, most often occurring in the titration period. The two most common TEAE leading to discontinuation during the treatment period were dizziness and abnormal coordination. Consistent with previous clinical trials, adverse effects were dose related.

Despite positive efficacy results in these trials, one major limitation is the short trial period of 12 weeks. Additionally, the data from the per protocol analysis has limited utility due to the high drop-out rates. This trial further reinforces the conclusion that lacosamide 400mg/day has improved clinical utility over the 600mg/day dose. When comparing response rates and seizure frequency, both 400mg/day and 600mg/day doses had similar outcomes with more documented adverse events at the higher dose. The investigators concluded that the 600mg/day dose may provide an additional benefit over lacosamide 400mg/day for patients able to tolerate the higher dose.

For more information on the above clinical trials, refer to *Appendix A*.

Chung *et al*. Pooled analyses[8]

This pooled analyses analyzed the three pivotal clinical trials[5,6,7] discussed above. It is a post hoc analysis that was conducted to assess response during the titration phase and evaluate other concomitant AEDs

used. It included a total of 1294 patients that received at least one dose of trial medication and had at least one post baseline efficacy assessment. Most patients (84%) were receiving two to three concomitant AEDs: carbamazepine (35%), lamotrigine (31%), levetiracetam (29%), valproate (23%), and topiramate (22%).

Table 5 Results to Chung P. *et al* Pooled Analyses

	Median % Reductions in Seizure Frequency Per 28 Days* (ITT)	50% responders* (ITT)	75% responders* (ITT)
Placebo	18.4%	22.6%	9.2%
Lacosamide 200mg/day	33.3% (p<0.05)	34.1% (p<0.05)	13.5%
Lacosamide 400mg/day	36.8% (p<0.001)	39.7% (p<0.001)	19.1% (p<0.001)
Lacosamide 600mg/day	39.4% (p<0.001)	39.6% (p<0.001)	18.8% (p<0.001)

*p values compared to placebo

When analyzed by concomitant AED, lacosamide treatment showed a reduction in seizures, regardless of the concomitant AED used. Three serious adverse were reported to have occurred at an overall rate of ≥ 1% in any treatment group: dizziness (1.5% for lacosamide 600 mg/day vs 0% for all other groups), nystagmus (1.0% for lacosamide 600 mg/day vs 0% in all other groups) and convulsion (1.1% for lacosamide 200 and 400 mg/day, 0% for lacosamide 600 mg/day vs 0.8% for placebo).

***Intravenous efficacy*[9-11]**

Three clinical trials were published to support the tolerance, safety, and efficacy of IV lacosamide.

Biton *et al.*[9]

The first clinical trial by Biton, et al. assessed whether intravenous lacosamide can be used as a replacement for oral lacosamide. It was a multicenter, double-blind, double-dummy, randomized, inpatient study. Primary endpoints were to evaluate the safety and tolerance of intravenous versus oral lacosamide. The secondary endpoint was to assess the pharmacokinetic profile of intravenous lacosamide.

There were 60 patients enrolled in the study. Patients were randomized in a 2:1 ratio to either the intravenous lacosamide and oral placebo group or the intravenous placebo and oral lacosamide group. All medications were given twice daily. Each group was then separated by infusion rate subsets: 60 minutes versus 30 minutes. Inclusion criteria included stable doses of oral lacosamide (200 to 600mg/day) and concomitant AEDs, acceptable candidates for venipuncture and intravenous infusion, normal platelet count, and stable vagus nerve stimulation for the previous two weeks. Some of the exclusion criteria included pregnant women, recent blood donor, recent participation in an investigational trial, patients that violated the open-label trial, sitting diastolic BP outside the range of 50-105 mmHg or a resting pulse that was outside the range of 50-110 bpm. Patients enrolled in an open label 8 week trial where they received oral lacosamide. The infusion treatment period was for two days. Primary endpoints were assessed based on adverse events, vital signs, 12-lead electrocardiogram reading (ECG), laboratory results, physical exam, and neurological exam. Blood samples were collected at different times (during IV infusion, after infusion, and at different times during the second day of infusion) to evaluate the pharmacokinetic properties of intravenous lacosamide. Seizure counts were analyzed to assess efficacy of the intravenous lacosamide compared to the oral form. The intravenous dose was the same as the lacosamide oral dose.

Forty-three percent of patients took one concomitant AED and 57% took two concomitant AEDs. There were 29% of patients receiving doses greater than 400mg/day who experienced mild adverse effects after initiation of the first intravenous infusion. There were no changes in vital signs and number of seizures compared to the oral lacosamide. There were minimal changes in ECGs. A small increase in the mean PR

interval was found in both oral and intravenous lacosamide. There were no changes in pharmacokinetics when lacosamide was infused over 60 minutes versus 30 minutes. The bioavailability of oral lacosamide was comparable to the intravenous lacosamide. (AUC of oral lacosamide was 33.55-38.6, AUC of intravenous lacosamide was 36.9-40.18 and the ratio for IV to oral was approximately 100%). Intravenous lacosamide infused in 60 minutes and 30 minutes showed the same safety, tolerance, and pharmacokinetic profile as the oral lacosamide.

Lacosamide blood levels were closely tested to evaluate the bioavailability of the drug. Unfortunately, the sample size of the concomitant AEDs was too small to evaluate its effects on the plasma concentration of lacosamide. There was no statistical testing conducted therefore the strength of the results was not assessed.

Krauss *et al.*[10]
A second clinical trial evaluated the safety and tolerability of three different intravenous lacosamide infusion durations. The study was a multicenter, open-label, inpatient trial conducted at 17 sites. Study participants were previously on a stable oral regimen of lacosamide for at least two weeks prior to the trial. The dose of intravenous lacosamide was the same dose as the stable oral dose. Subjects were separated into three different infusion groups: 30 minute group (n=40), 15 min group (n=100) and 10 minute group (n=20). Lacosamide was infused twice daily. The primary endpoints were to evaluate the safety and tolerance of each infusion rate. The study monitored adverse events, vital signs, change in electrocardiography (EKG), physical and neurological exams, laboratory test values and number of seizures. Blood samples were drawn 20 minutes before infusion and at the end of the infusion to measure the trough concentration and maximum concentration respectively. Adverse reactions were monitored daily for a total of 5 days. A majority of the patients were treated with other AEDs including levetiracetam, carbamazepine, lamotrigine, and valproate. Ninety-six percent of the patients received lacosamide 200-600mg/day, while others received lacosamide 700-800mg/day.

The results showed that adverse events did not increase with shorter infusion durations. The most common adverse events were headache (7%), dizziness (6%), and diplopia (4%). Patients that received 500-800mg/day complained of adverse events related to the nervous system (eg. headache and dizziness). Intravenous lacosamide was discontinued in two patients due to adverse events. Four patients in the 30 minute infusion group incorrectly received 800-1000mg/day dose for two days. Of these, only one patient complained of headache and the other three patients denied any adverse events. One patient in the 15 minute infusion group complained of bradycardia. However, it was noted that the patient was on a beta blocker. There were no changes in vital signs (except for the patient with bradycardia), EKG, laboratory tests and number of seizures. There were also no changes in the plasma concentrations of lacosamide between the different infusion groups. The study concluded that intravenous lacosamide was equivalent to oral lacosamide in regards to bioavailability, pharmacokinetics and tolerability. There was no difference in the safety profile between the different infusion groups. There was no increase in adverse events when the IV medication was given during a five day period.

This clinical study enrolled more subjects thus increasing the chance of obtaining avalid result. The study showed similar adverse events when compared to oral lacosamide trials. Both intravenous and oral lacosamide showed that adverse events were mostly found in patients taking doses greater than 400mg. The treatment period was longer compared to the Biton et al study. One limitation of this study was the lack of blinding which can increase the chance of bias. Another limitation was the lack of consistency in regards to the adjunct AEDs received by the subjects since this may affect the lacosamide concentration. Tolerability, safety and efficacy may vary depending on the combination of medications. The sample size was not based on any statistical value such as power. There was no statistical analysis to detect whether the results were statistically relevant.

Parkerson *et al.* [11]

The safety, tolerability, and efficacy of IV lacosamide were evaluated in a retrospective case series consisting of 17 critical ill patients by Parkerson et al. The study population included patients with acute recurrent seizures or periodic epileptiform activity captured during continuous electroencephalogram (EEG) monitoring. Seizures occur frequently in critically ill patients and IV formulations of AEDs are often necessary due to rapid delivery and a more predictable pharmacokinetic profile.

In this study, 37 patients were screened with 17 included in the analysis. Inclusion criteria included a marked change in EEG from baseline while on continuous monitoring, refractory to at least one AED, and newly started on lacosamide. Nine patients received lacosamide as the second AED, six patients as the third AED, one patient as the fourth AED, and one patient as the fifth AED. Levetiracetam was the initial AED in 64.7% (11/17) of the patients as it has been shown to be safe and effective in critically ill patients. Due to the retrospective nature of this study, the dose of lacosamide varied from 50mg twice daily at initiation and up to 200mg twice daily after titration.

After the initiation of lacosamide, improvement was observed between 7 to 45 hours for 70.6% (12/17) of the patients. For two patients, other AEDs were added due to persistent seizures. No improvement in EEG was noted in one patient. Lacosamide was continued for all 17 patients for the remainder of the hospitalization as no complications directly attributable to lacosamide were noted. Eleven of the 17 patients were discharged from the hospital on lacosamide, four expired, one was discharged to hospice care, and the last patient was weaned off lacosamide and discharged on phenytoin monotherapy.

In an effort to compare lacosamide with other AEDs, the same method was applied to patients on phenytoin and valproic acid with response rates of 66.7% (6/9) and 30.8% (4/13) respectively. While this study may provide some insight to IV lacosamide, there were many limitations aside from the obvious short duration and limited patient population. A case series study has limited applicability due to the many possible confounders. In this study, the true efficacy of lacosamide versus the original AED(s) cannot be teased out. Additionally, seizure improvement may have been partially attributed to patient clinical status. While data suggest better response rates with lacosamide over phenytoin and valproic acid, this conclusion cannot be drawn due to the small and variable patient samples in clinical trials. Future studies directly comparing levetiracetam and lacosamide would be beneficial as both agents have minimal drug interactions, low protein binding, are well tolerated, and have proven efficacy as adjunct therapy for partial onset seizures. Based on this study alone, IV lacosamide can only be recommended as an adjunct to levetiracetam or other AEDs at this time.

Diabetic Neuropathy:[12-16]

Peripheral diabetic neuropathy is a common complication in patients with diabetes and has a negative influence on quality of life due to changes in sleep, mood, mobility, and daily activity. Current pharmacological options for the management of diabetic peripheral neuropathy include: analgesics, antidepressants, opioids, and anticonvulsants. On average, anticonvulsants provide 50% pain relief in 63% of patients. Lacosamide is a new investigational anticonvulsant for the treatment of peripheral diabetic neuropathy.

Efficacy measures

- Clinical Global Impression of Change (CGIC) – The CGIC is a subjective outcome measure for overall pain on a 7-point categorical scale ranging from "much better" to "much worse."
- Neuropathic Pain Scale (NPS) – The NPS is an 11-item scale that is classified as sharp, hot, dull, cold, sensitive, itchy, deep, and surface.
- Patient Global Impression of Change (PGIC) – The PGIC is a subjective outcome measure for overall pain on a 7-point categorical scale ranging from "much better" to "much worse."

- 11-Point Likert Pain Score – The 11-Point Likert Pain Scale is often used as a primary efficacy measure. It is an 11-item rating scale ranging from 0 (no pain) to 10 (greatest possible pain). A reduction of at least 2 points is frequently observed as a response to treatment.
- 11-Point Numeric Pain Rating Scale (NPRS) – The 11-Point NPRS is often used as a primary efficacy measure. It measures the change in average daily (24-hour) pain scores ranging from 0 (no pain) to 10 (worst possible pain) from baseline to the endpoint.
- Short-Form-36 Quality of Life Questionnaires (SF-36) – The SF-36 is a 36 question survey based on a patient's mental health and physical health.
- Short Form-McGill Pain Questionnaire (SF-MPQ) – The SF-MPQ includes a pain rating scale, a visual analog scale of overall pain, and a 6-point present pain intensity scale.

Rauck *et al.*[12]

The first trial was a phase-2, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in patients with peripheral diabetic neuropathy. Persons 18 years of age and older with a diagnosis of diabetes, painful peripheral diabetic neuropathy, HbA1C ≤ 10% for at least 3 months, 1-5 year history of moderate to severe neuropathic pain, and a score of at least 4 on the Likert pain scale were eligible to participate. Acetaminophen 2 grams/day was allowed as analgesic rescue medication. Participants were randomized to receive placebo or lacosamide 400 mg/day. Lacosamide was initiated at 100 mg/day for 3 weeks and then titrated by 100 mg/day in weekly intervals. If dose reduction was needed, the investigator was able to do so. The study's primary outcome measure was the mean change from baseline to study endpoint in the 11-point Likert pain score. Secondary measures were the mean changes in Short Form-McGill Pain Questionnaire (SF-MPQ) and Short-Form-36 Quality of Life Questionnaires (SF-36), Patient and Clinical Global Impression of Change (PGIC, CGIC). Safety endpoints included adverse events, changes in laboratory values, QT interval, and vital signs.

One hundred and nineteen patients were randomized to the treatment groups. Forty six patients in the treatment arm and forty eight patients in the placebo arm completed the study. Patients in the lacosamide group received the study medication for up to 82 days. Forty two patients received the maintenance dose of 400 mg/day for an average of 27.6 days. Lacosamide had significantly better pain relief versus placebo on the Likert pain scale (-3.11 versus -2.21, p=0.039, respectively). A reduction in the pain score by at least two points was seen in 60% of patients in the lacosamide group compared with 50.8% in the placebo group. Lacosamide resulted in a higher proportion of pain-free days (18.1%) compared with the placebo group (7.5%). During the maintenance period, 13 patients in the lacosamide group used rescue analgesics for 59% of the days and 21 patients in the placebo group used them for 67% of the days. SF-MPQ was significantly reduced from baseline versus placebo (50% pain relief versus 36%, p=0.0477, respectively). SF-36 was significantly improved in the lacosamide group versus placebo and both PGIC and CGIC ratings favored lacosamide. Results comparing changes from baseline in daily Likert pain scores are listed in Table 6.

Table 6 Analysis of Covariance Analysis of Changes in Likert Pain Least Squares Mean Scores from Baseline to End Point (Last Observation Carried Forward Analysis)

Treatment	n	Pain Scores		Endpoint Least Squares Mean	Treatment Difference Compared to Placebo
		Baseline	End Point		
Placebo	59	6.5	4.5	-2.21	
Lacosamide	60	6.6	3.7	-3.11	0.9 (p=0.039)

The most common adverse events were comparable in both groups. The most frequently reported side effects were headache, dizziness, nausea, and diarrhea.

In conclusion, this phase-2 trial demonstrated that lacosamide improved scores on pain scales used in diabetic neuropathic pain when compared to placebo, but with several limitations. One limitation to the

trial was that the diagnosis of diabetic neuropathy was determined by clinical examination and not by nerve electrophysiology studies. Also, the primary outcome measure was compared to placebo and not to standard treatments. It is expected that larger scale trials with lacosamide will address the comparison to standard treatments and not to placebo. Additional studies are needed to determine its place in therapy as compared to other currently available treatments.

Wymer *et al.*[13]
The second study was a randomized, placebo-controlled, double-blind, parallel-group, multicenter trial in patients with diabetic neuropathy. Persons 18 years and older with a diagnosis of type 1 or type 2 diabetes mellitus, HbA1c below 12%, optimized plasma glucose values for 3 months, and symptoms of painful diabetic neuropathy for 6 months to 5 years were eligible to participate. Patients were also allowed to utilize acetaminophen up to 2 grams/day as a rescue medication during the trial. The trial consisted of a 2-week run-in period followed by an 18-week double-blind phase. The first week of the run-in was a wash out period and the second week was the baseline phase for pain assessments. Patients were randomized to receive placebo or lacosamide 200, 400, or 600 mg/day in a 1:1:1:1 fashion. The treatment phase consisted of a six week titration phase followed by a twelve week maintenance phase. In the titration phase, lacosamide 50 mg was initiated and then escalated in weekly increments by 100mg to the assigned dose.

The study's primary outcome measure was the mean change from baseline to the last 4 weeks of the maintenance phase using the 11-point Likert pain scale. Secondary measures included the mean changes from the baseline week to the entire titrations phase, entire maintenance phase, and the entire treatment phase. Additional secondary measures included the mean changes in the Patient Global Impression of Change (PGIC). The safety endpoints included adverse events, changes in hematology, blood chemistry, urinalysis, ECGs, vital signs, physical and neurologic examinations, plasma concentrations of lacosamide at each visit, and changes in fibular head to ankle peroneal nerve motor conduction velocity and bilateral sural nerve sensory conduction tests to determine the safety on nerve function.

Many patients reported previous use with other medications to treat neuropathic pain with reported failure to achieve adequate pain relief, 67% of patients reported a previous use of 1 or more medications to treat neuropathic pain. The most common prior medications were gabapentin (34%), amitriptyline (14%), and opioids (10%). 38% of patients reported previously using anticonvulsants, anti-inflammatory agents, or acetaminophen. However, the majority of patients reported failure to achieve adequate pain relief.

An analysis of the Likert pain scale from baseline to the last 4 weeks of the maintenance phase demonstrated a significant difference between the lacosamide 400 mg/day group and placebo; however, the 200 mg/day and 600 mg/day groups did not achieve statistical significance. The mean daily pain score decreased by 2.5 points (from 6.5 to 4) in the lacosamide 400mg/day group versus the placebo group's reduction of 1.8 points (from 6.6 to 4.8). Additionally, the lacosamide 400 mg/day group was significantly more efficacious than the placebo group for the entire treatment phase ($p<0.01$), titration phase ($p=0.01$), and the maintenance phase ($p=0.02$). PGIC ratings favored the lacosamide 400 mg/day group. Results comparing changes from baseline in daily Likert pain scores are listed in Table 7.

Table 7 Statistical Analysis of Changes from Baseline in Daily Likert Pain Scores

Change from Baseline	Treatment Group	n	Endpoint Least Squares Mean	Comparison	Treatment Difference
Primary Endpoint: Last 4 weeks of the maintenance phase	Placebo	90	-1.60		
	200 mg/day	92	-1.99	200 mg vs. placebo	-0.39 (p=0.19)
	400 mg/day	91	-2.34	400 mg vs. placebo	-0.74 (p=0.01)
	600 mg/day	92	-2.02	600 mg vs. placebo	-0.42 (p=0.16)
Maintenance Phase	Placebo	73	-1.65		

	200 mg/day	79	-1.93	200 mg vs. placebo	-0.28 (p=0.36)
	400 mg/day	72	-2.39	400 mg vs. placebo	-0.74 (p=0.02)
	600 mg/day	54	-2.55	600 mg vs. placebo	-0.90 (p<0.01)

Two hundred thirty five patients (64%) completed the 12-week maintenance phase. Completion rates were as follows: 67 of 93 in the placebo group, 69 of 93 in the lacosamide 200mg/day group, 56 of 91 in the lacosamide 400mg/day group, and 42 of 93 in the lacosamide 600mg/day group. The most common reason for premature discontinuation of treatment was due to adverse events: placebo (8 patients), lacosamide 200 mg (8 patients), lacosamide 400 mg (21 patients), and lacosamide 600 mg (37 patients). Patients that discontinued treatment due to adverse events were 9% in the placebo group, 9% in the 200 mg/day group, 23% in the 400mg/day group, and 40% in the 600 mg/day group.

The most common adverse events included dizziness, nausea, fatigue, headache, and tremor. They appeared to be dose related. Most adverse events were mild or moderate in severity. Serious adverse events occurred in 7%, 3%, 10%, and 10% in patients randomized to the placebo, 200 mg/day, 400 mg/day, and 600 mg/day groups, respectively. Coronary artery disease was reported in two patients. One event was fatal; a 45 year/old male experienced ventricular fibrillation and died after 9 days of lacosamide 200 mg/day therapy. It was considered a natural death and not related to the study medication. Adverse events that led to study discontinuation were dizziness, nausea, and balance disorder. Abnormal liver function tests were recorded in some patients, but were similar among the 4 treatment groups. The results from the ECGs showed no effect on heart rate or QTc interval. A small dose related increase was observed in the mean PR interval. The incidence of treatment emergent first-degree heart block was similar between the groups. There was a slight increase in QRS duration in the lacosamide groups. There was no change in peroneal nerve conduction velocity between the treatment groups.

In summary, this trial found that lacosamide administered as monotherapy at a daily dose of 400 mg/day is efficacious in reducing pain scale scores in diabetic neuropathy. However, a limitation to the study was that it did not compare lacosamide to an alternative agent approved or proven to work in the treatment of diabetic peripheral neuropathy. The most common side effects were rated mild to moderate in severity. Future studies should compare the efficacy of lacosamide to currently approved treatments for diabetic neuropathy.

Ziegler *et al.*[14]
The third study was an 18 week, double-blind, placebo-controlled trial in patients with diabetic neuropathy. Persons 18 years and older with a diagnosis of type 1 or type 2 diabetes, symptomatic diabetic peripheral neuropathy for 6 months to 5 years, and an A1C<12% were eligible to participate. Acetaminophen ≤ 2 grams/day were allowed as a rescue medication. Patients were randomized to 1:2:2 a ratio to placebo, oral lacosamide 400 mg/day, or lacosamide 600 mg/day. The lacosamide 400 mg/day group received a slow titration of 100 mg/day for 3 weeks, followed by weekly increases of 100 mg/day, to a target dose by week 6 of 400 mg/day or to a standard titration of 100 mg/day with weekly increases of 100 mg/day to the target dose by week 4-6 of 400 mg/day. The 600 mg/day group followed the standard titration by increasing the dose by 100 mg/day each week.

Three hundred fifty seven patients were randomized and 246 patients completed the trial. There were no differences between baseline characteristics; however, there were numerically more patients in the placebo group that reported severe pain at baseline.

The study's primary outcome measure was the change in the average daily pain score from baseline to the average score over the last 4 weeks of the maintenance period with the 11-point Numeric Pain Rating Scale (NPRS). Secondary measures included the percentage of patients with a ≥ 2 point or ≥ 30% reduction in Numeric Pain Rating Scale, the change in the Short Form McGill Pain Questionnaire (SF-

MPQ), Patient's Global Impression of Change (PGIC), and the change in the Neuropathic Pain Scale (NPS). The safety endpoints included adverse events, withdrawal, laboratory changes, electrocardiogram changes, vital signs, and changes in physical/neurological examinations.

Pain scale scores reductions were slightly higher in the 600 mg/day group than in the 400 mg/day group, but there were higher dropout rates and rates of adverse events with the 600 mg/day group. Results comparing the treatment difference in reducing average daily pain scores are listed in Table 8.

Table 8 Change from Baseline in Numeric Pain Rating Scale Scores

Change from Baseline	Treatment Group	n	Endpoint Least Squares Mean	Treatment Difference Compared to Placebo
Primary Endpoint: Last 4 weeks of the maintenance phase	Placebo	74	-1.50	
	400 mg/day	149	-1.90	-0.40 ± 0.26 (p=0.12)
	600 mg/day	132	-1.86	-0.36 ± 0.27 (p=0.18)
Titration Period (6 weeks)	Placebo	74	-0.61	
	400 mg/day	149	-0.95	-0.34 ± 0.16 (p=0.03)
	600 mg/day	132	-1.07	-0.46 ± 0.16 (p<0.01)
Maintenance Period (12 weeks)	Placebo	74	-1.40	
	400 mg/day	149	-2.05	-0.66 ± 0.26 (p=0.01)
	600 mg/day	132	-2.19	-0.79 ± 0.28 (p<0.01)
Treatment Period (18 weeks)	Placebo	74	-1.05	
	400 mg/day	149	-1.50	-0.44 ± 0.20 (p=0.03)
	600 mg/day	132	-1.52	-0.47 ± 0.21 (p=0.02)

The most common dose-related adverse events included dizziness, nausea, vertigo, headache, and vomiting. There were no findings of significant changes in laboratory levels, vital signs, body weight, or findings from physical and neurological examinations.

In conclusion, lacosamide did not result in a significant reduction in pain over placebo for the primary outcome; however, it demonstrated a significant reduction in pain during the titration, maintenance, and treatment period. There were also improvements that were observed in the PGIC, VAS, and pain interference with sleep and daily activities.

Nonconvulsive Status Epilepticus: [15-17]

Status epilepticus is a neurological emergency most often requiring immediate treatment with intravenous agents. Recommended first line agents are benzodiazepines, preferably lorazepam, followed by phenytoin. Additional therapies for refractory status epilepticus include barbiturates, propofol, or midazolam . These agents routinely require patients receive artificial ventilation and intensive therapy. Nonconvulsive status epilepticus (NCSE) is defined as behavioral or cognitive change lasting for at least 30 minutes with EEG evidence of seizure activity. A less aggressive approach is usually taken for patients with NCSE. Valproate and levetiracetam are two anticonvulsants available as intravenous formulations considered therapeutic options in the management of nonconvulsive status epilepticus. Minimal data is available to support the use of intravenous lacosamide for NCSE. A number of case reports have been published using lacosamide in NCSE when drug-drug interactions or allergies prevent the use of currently recommended first line agents.

Kellinghaus et al [16]

Case report of a 42 year old female who suffered from an episode of left hemispheric status epilepticus provoked by irregular intake of her anticonvulsant medications. Lorazepam was administered on 2 different occasions, 10 minutes apart without any cessation of epileptiform activity. Patient became sedated and respiratory rate declined supporting the avoidance of further dose titration of barbiturates. The use of phenytoin and valproate were not desirable due to potential drug interactions with patients'

existing drug therapy. The patient had history of psychotic adverse effects to levetiracetam and as a result , this agent was also avoided. Lacosamide was administered as a 200mg bolus dose and within 3-5 minutes epileptiform activity ceased. A mild rash was reported which resolved in 2 days with appropriate treatment but was unable to be definitively attributed to lacosamide. No other complications were reported regarding the use of lacosamide.

Albers et al [17]
Case reports of seven patients who were successfully treated with intravenous lacosamide. All patients received levetiracetam or valproic acid, or both, in combination with topiramate, benzodiazepines, and propofol without cessation of epileptiform activity. With intravenous lacosamide administration, epileptiform activity resolved within 24 hours in all patients. All patients were simultaneously receiving antiepileptic drugs. No complications were reported in any of the patients regarding the use of lacosamide.

In conclusion, lacosamide may be a therapeutic alternative if other agents fail to achieve cessation in epileptiform activity or are considered therapeutically inappropriate options. Additional large prospective studies are needed to assess the safety and efficacy of the use of lacosamide in the treatment of NCSE.

Adverse Events (Safety Data)[1,2,5,8,9,18-20]

Deaths and Other Serious Adverse Events

No deaths have been reported to be associated with the use of Lacosamide.

Atrial fibrillation and atrial flutter

The package insert warns of atrial fibrillation or flutter in 0.5% in trials of subjects with diabetic neuropathy. In a case report, a patient was initiated on lacosamide and titrated appropriately to 600mg/day. Prior to lacosamide, the patient had no history of cardiac disease, palpitations, or arrhythmias. Three months later, the patient developed atrial flutter. Lacosamide was decreased to 400mg/day however: atrial flutter persisted. After evaluation, atrial flutter had resolved post discontinuance of lacosamide.

Common Adverse Events

Table 9 Adverse events ≥ 5 % formatted from pooled analyses Chung *et al*

Adverse event	Lacosamide 200 mg/day %	Lacosamide 400 mg/day %	Lacosamide 600 mg/day %	Placebo %
Dizziness	16	**30**	53	8
Headache	11	**14**	12	9
Nausea	7	**11**	17	4
Diplopia	6	**10**	16	2
Blurred vision	2	**9**	16	3
Vomiting	6	**9**	16	3
Somnolence	5	**8**	8	5
Fatigue	7	**7**	15	6
Ataxia	4	**7**	15	2
Tremor	4	**6**	12	4
Diarrhea	3	**5**	4	3
Nystagmus	2	**5**	10	4
Balance disorder	1	**5**	6	0

Other Adverse Events

- Blood and lymphatic system disorders: neutropenia, anemia
- Cardiac disorders: palpitations
- Ear and labyrinth disorders: tinnitus

- Gastrointestinal disorders: constipation, dyspepsia, dry mouth, oral hypoaesthesia
- General disorders and administration site conditions: irritability, pyrexia, feeling drunk
- Injury, poisoning, and procedural complications: fall
- Musculoskeletal and connective tissue disorders: muscle spasms
- Nervous system disorders: paresthesia, cognitive disorder, hypoaesthesia, dysarthria, disturbance in attention, cerebellar syndrome
- Psychiatric disorders: confusional state, mood altered, depressed mood

Tolerability
Among subjects with partial-onset seizures in the clinical trials, 1.2% assigned to placebo and 15.3% assigned to lacosamide discontinued due to medication-associated adverse reactions. Nine of the 418 subjects that were randomized to lacosamide discontinued while still receiving placebo during the titration period.

Among subjects with partial-onset seizure, 2.9% assigned to the 200 mg/day lacosamide, 4.8% assigned to the 400 mg/day lacosamide, and 7.7% assigned to 600 mg/day lacosamide discontinued due to adverse events. Subjects were more likely to discontinue a medication due to drug-related adverse effects at higher doses and adverse effects were more likely to occur on the onset of titration. The most common adverse reactions associated with discontinuation in subject treated with lacosamide (rates of at least 5%) were dizziness, nausea, ataxia, vomiting, and nystagmus. No subject experienced a serious adverse event (frequency of greater than 1% of all patients). The most commonly reported serious adverse event was dizziness and convulsions and the frequency was the same among all groups (5% assigned to placebo, 9% assigned to 200 mg/day lacosamide, 6% assigned to 400 mg/day lacosamide, and 3% assigned to 600 mg/day).

Among subjects with partial-onset seizure, 0% of the patients withdrew due to adverse events. Only 1.7% of patients receiving IV lacosamide withdrew, but that was because no vascular access was available. Twenty nine percent of those assigned to lacosamide 400 mg/day or more compared with 21% assigned to lacosamide less than 400 mg/day experience at least one medication-related adverse event. The most commonly reported medication-related event reported was dizziness and all adverse events were mild to moderate in intensity. Medication-related adverse events were more common with faster infusion time, 25% assigned to IV lacosamide with a 60-minute infusion compared to 32% assigned to IV lacosamide with a 30- minute infusion. IV lacosamide also had a slightly higher incidence over oral medication, with 30% assigned to oral lacosamide with IV placebo over 60-minute infusion versus 25% assigned to IV lacosamide over 60-minute infusion with oral placebo and 18% assigned to oral lacosamide with IV placebo 30-minute infusion compared to 32% IV lacosamide 30-minute infusion with oral placebo.

Warnings and Precautions[1,2]

Suicidal behavior and Ideation
Antiepileptic drugs (AEDs) have been shown to increase the risk of suicidal thoughts or behavior. Pooled analyses of 11 different AEDs showed that patients taking these agents are at a great risk of suicidal thinking or behavior compared to placebo. These suicidal thoughts or behaviors were observed as early as one week after initiation of treatment with AEDs. Most clinical trials included in the analysis did not extend beyond 24 weeks and could therefore not be assessed beyond 24 weeks. Due to these previous analyses, risk versus benefits should be considered when using lacosamide or any other AEDs. Patients should be monitored for signs and symptoms of suicidal behavior and ideation closely.

PR interval prolongation
A dose-dependent increase in PR interval was observed in patients treated with lacosamide in clinical trials. Asymptomatic first-degree atrioventricular (AV) block was observed as an adverse reaction in 0.4% of patients receiving lacosamide and 0% of patients receiving placebo. Use of lacosamide should be

monitored for PR prolongations, especially when given with other medications that prolong PR interval. An ECG should be obtained at baseline and after titration of lacosamide. It should be used with caution in patients with conductions problems or severe cardiac disease such as myocardial ischemia or heart failure.

Atrial fibrillation and atrial flutter
Atrial fibrillation or atrial flutter was observed in 0.5% of patients with diabetic neuropathy receiving lacosamide compared to 0% of patient receiving placebo. Caution should be used when using lacosamide in patients predisposed to atrial fibrillation or atrial flutter especially patients with diabetic neuropathy.

Pregnancy and breast feeding
Lacosamide is Category C and it is recommended that women do not breast feed since infant risk cannot be ruled out. Studies in lactating rats have shown that lacosamide and/or its metabolites are excreted in milk. It is not known whether lacosamide is excreted in human milk.

Other warnings and precautions consistent with AEDs
- Multi-organ hypersensitivity reactions
- Not recommended for use in patients with severe hepatic impairment
- Use caution and carefully dose titrate in patients with renal impairment (CrCl ≤30mL/minute)
- Do not abruptly discontinue due to risk of increased seizure frequency
- Caution phenylketonurics. Lacosamide oral solution contains aspartame, a source of phenylalanine.

Contraindications [1,2]
None according to the package insert.

Drug Abuse and Dependence[1,2,21]
Lacosamide is classified in the U.S. as a controlled substance schedule V. Lacosamide mechanism of action and properties are not known to be associated with abuse potential, but there is a possibility due to its centrally acting mechanism of action.

In a published case report related to lacosamide intoxication in attempted suicide, a patient ingested 12 g of lacosamide, 56 g of gabapentin, 2 g of topiramate, and 2.8 g of zonisamide. It was concluded that intoxication with lacosamide, in combination with overdoses of multiple AEDs, can be survived even after ingestion of 30 times the maximum recommended daily dose of lacosamide. Lacosamide may have contributed to the prolongation of the PR interval; however, this was not associated with second-degree or higher atrioventricular block or with any related clinical symptoms. Lacosamide might have also contributed to the patient's hypotension that occurred 4 hours after ingestion however it may have been associated with the administration of benzodiazepines for the post overdose seizures. Also note that the patient ingested multiple AEDs which made it difficult to credit some of the toxicity symptoms experienced to a specific AED.

There is currently no specific antidote for overdose of lacosamide.

Post marketing Adverse Events[1,2,22]
Post marketing adverse events identified post approval use of lacosamide includes body weight loss, gait instability, bradycardia, and rash.

A small 6 months post marketing retrospective review was conducted on 25 patients up to 24 weeks after initiation of adjunctive lacosamide. Patients were titrated to an initial target of 400mg/day; however, alterations were made based on provider's discretion. The most commonly prescribed anticonvulsants were lamotrigine, levetiracetam, carbamazepine, and zonisamide. At the end of six months, eight patients

(32%) reported a greater than 50% reduction in seizure frequency, similar to data from previously reported clinical trials. Three patients (12%) had a reduction greater than 90%. Of note, one patient who was prescribed pregabalin and had lacosamide substituted for lamotrigine had a 100% increase in seizure frequency. Thirteen patients (52%) reported side effects during the titration. In 5 patients (20%), these disappeared during the maintenance phase or with dose reduction. Two patients (8%) lost more than 10% of their body weight. One patient experienced a rash that resolved when changed from tablets to the oral suspension formula of lacosamide. This post marketing data is indicative that lacosamide efficacy and adverse events are similar to those of the previous completed clinical trials.

Look-alike / Sound-alike (LA / SA) Error Risk Potential [1,2,23-25]

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

- LA/SA for generic name lacosamide: *zonisamide, glucosamide, loperamide*
- LA/SA for trade name Vimpat®: *Vimovo*

Drug Interactions[1,2,23]

Drug-Drug Interactions

Lacosamide has the potential to inhibit CYP 2C19.

- *Digoxin*: lacosamide had no influence in the pharmacokinetics of digoxin
- *Metformin*: lacosamide had no clinically relevant changes in metformin levels; metformin did not affect pharmacokinetics of lacosamide
- *Omeprazole*: plasma levels of lacosamide metabolite were reduced by 60% when concomitantly used with omeprazole
- *Oral contraceptives*: lacosamide had no influence on the pharmacodynamics and the pharmacokinetics of 0.03mg ethinyl estradiol and 0.15mg levonorgestrel except a 20% increase in C_{max} of ethinyl estradiol.

In placebo controlled clinical trials, the plasma concentrations of other AEDs (levetiracetam, carbamazepine, lamotrigine, topiramate, oxcarbazepine, phenytoin, valproic acid, phenobarbital, gabapentin, clonazepam, and zonisamide) were not affected by the concomitant use of lacosamide. A small decrease of 15-20% was observed in the plasma concentration of lacosamide when concomitantly used with carbamezapine, phenobarbital, or phenytoin.

Drug-Lab Interactions

Abnormal liver function tests were observed in controlled trials in patients who were concomitantly taking 1-3 AEDs. Liver function enzymes elevations greater than 3 times the upper limit of normal were found in 0.7% of patients taking lacosamide versus 0% of those taking placebo. There was a report of hepatitis with greater than 20 times the upper limit of normal which occurred 10 days after lacosamide treatment was completed. Levels returned to normal within 1 month without specific treatment and were interpreted to be a delayed hypersensitivity reaction to lacosamide.

Acquisition Cost[4,15 -17]

Table 10 Cost comparison of Lacosamide and other AEDs

Antiepileptic Drug (AEDs)	Maximum Dose	Cost/Maximum daily dose/patient($)	Cost/Year/patient($)
Third Generation AED			
Partial seizure medications that affect voltage sensitive sodium channels			
Lacosamide (oral)	400mg/day	$9.37	$3418.74
Lacosamide (IV)	400 mg/day	$38.04	

Second Generation AEDs			
Partial seizure medications that affect voltage sensitive sodium channels			
Lamotrigine*	Max: 325mg/day	$0.12	$42.19
Levetiracetam*	Max: 3000mg/day	$0.72	$264.11
Oxcarbazepine*	Max dose: 2400mg/day	$1.57	$572.32
Topiramate*	Max dose: 400mg	$0.50	$182.65
Other second generation AEDs			
Felbamate	Max: 3600mg/day	$9.95	$3632.55
Gabapentin*	Max: 3600mg/day	$1.00	$361.68
Pregabalin	Max: 600mg/day	$2.99	$1090.04
Tiagabine	Max: 56mg/day	$18.99	$6931.33
Vigabatrin	Max: 3000mg/day	$110.03	$40,161.32
Zonisamide*	Max: 400mg/day	$6.81	$2486.96
Neuropathic pain			
Amitriptyline*	Max dose: 150mg/day	$0.16	$58.70
Gabapentin*	Max dose: 3600mg/day	$1.00	$361.68
Duloxetine	Max dose: 60mg/day	$2.85	$1040
Pregabalin	Max dose: 300mg/day	$1.49	$543.85

Antiepileptic Drug (AEDs)	Recommended Dose	Cost per medication vial
Nonconvulsive status epilepticus		
Diazepam*	10mg/dose; repeat if seizure occurs	5mg/mL (2mL vial) FSS price $1.45
Lorazepam*	Bolus: 0.1mg/kg or 4mg Rate: 2mg/min	2mg/mL (10mL vial) FSS price $4.92
Phenobarbital*	Bolus: 20mg/kg Rate: 50mg/kg/min	65mg/mL Net price $1.50
Phenytoin*	Initial dose:15-20mg/kg Infusion rate max: 50mg/min	50mg/mL (5mL vial) FSS price $1.03
Lacosamide	200mg/dose may repeat	10mg/mL (20mL vial) FSS price $20.05

* Generic formulation available

Pharmacoeconomic Analysis[26]

No pharmacoeconomic analysis has been published

Conclusions[1,9,27]

Lacosamide is an AED that has been approved for the use as an adjunctive treatment in patients with partial onset seizures. In general, 30% - 40% of epileptic patients remain uncontrolled on AED monotherapy due intolerable side effects to therapy and/or non-adherence to their AED regimens.

Lacosamide demonstrated efficacy and safety as an adjunctive therapy in partial onset seizures. The efficacy of lacosamide was demonstrated across 3 randomized placebo controlled clinical trials. Lacosamide was associated with a significant reduction in seizure frequency and a significant high responder rate (defined as a reduction of at least 50% in seizure frequency from baseline) in the 400mg/day and 600mg/day regimens in comparison to placebo. The most common adverse events to lacosamide were mild to moderate in intensity and generally dose-related. Dose-related adverse events included dizziness, nausea, and vomiting.

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Prepared by: Desirea Broome, PharmD, Pharmacy Resident; Jennifer Carrillo, PharmD, Pharmacy Resident; Quyen Duong, PharmD, Pharmacy Resident; Deanna Mina, PharmD, Pharmacy Resident; Kimberly Schnacky, PharmD, Clinical Coordinator
Contact Person: Kathy Tortorice Pharm D BCPS

National Drug Monograph Addendum

Lacosamide (Vimpat®)

December 2015

VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current

Since the approval of lacosamide oral and intravenous dose formulations in October 2008, a new FDA indication has been approved. On September 1, 2014 the FDA approved lacosamide for monotherapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older. Additionally, significant evidence is developing on the role of lacosamide in the treatment of status epilepticus (particularly in nonconvulsive status epilepticus) and the potential for patients already on an anti-epileptic drug to be converted to lacosamide monotherapy.

Status Epilepticus[1-22]

The successful use of lacosamide to treat status epilepticus (SE) and refractory status epilepticus (RSE) has been reported in several case reports, case series, retrospective reviews and observational studies. Refer to **Table 1** for full details of these studies. There are several factors which can influence outcomes in RSE; duration of seizures, type of seizure (generalized tonic clonic, focal) current antiseizure medications and nature of seizure development (idiopathic, traumatic, post stroke) Trinka[14], et al; discussed 19 studies (ten single case reports and nine case series, reporting a total of 136 episodes of refractory SE (50 % NCSE, 31 % focal SE, and 19 % CSE) treated with lacosamide. This retrospective case series included patients with various forms of SE in different stages. The most commonly used bolus dose was 400 mg, followed by a daily dose of 200–400 mg lacosamide. The overall success rate was 56% (76/136). Paquette[15], et al, conducted a systematic review of the available evidence for lacosamide in SE and RSE. There were thirteen studies which met the criteria for review for patients with RSE. A total of 390 RSE patients were followed in these reports. The ability of lacosamide to terminate RSE, was described in one comparative cohort study which found no improvement in SE duration or seizure control with addition of lacosamide. Another study documented no difference compared to use of phenytoin. Eleven descriptive studies using lacosamide as add-on RSE therapy revealed seizure termination rates of 0–100% (median 64.7%).

An area where lacosamide may provide significant benefit is in the treatment of non-convulsive status epilepticus (NCSE). Belcastro[18], et al, reported on 16 patients (7 M/9 F; 77 ± 7 years of age) with NCSE. Lacosamide was initiated at a loading dose of 400 mg over 30 min, followed by a mean maintenance dose of 400 mg per day. Lacosamide was effective in treating NCSE in eight of the sixteen patients in whom epileptic activity disappeared (7/8) or was significantly reduced (1/8) within 45-60 min after administration. None of these patients relapsed in the following 24 h. No adverse events were observed.

Monotherapy

Monotherapy with lacosamide can involve different patient populations. These include patients who are treatment naïve, those who are switched to lacosamide monotherapy from other existing AED therapy and those who are begun on lacosamide adjunctive therapy and transitioned to lacosamide monotherapy.

A retrospectively chart review of patients with focal epilepsy on lacosamide included 66 patients with 18 patients in Group 1 (naive to antiepileptic drug (AED) therapy) and 48 patients in Group 2 (previously treated with AEDs).[23] Patients were followed up for 0.5-54 months in monotherapy (mean 15.5 months). Forty-two (63.6%) patients remained seizure-free during all the follow-up. At 6 and 12 months, seizure-free rates were 77.6% and 72.3%, respectively. No differences were found between Groups 1 and 2 regarding efficacy outcomes or tolerability issues.

Lattanzi, et al[24], reported on a study of 58 patients. All patients retained lacosamide at 1-year from withdrawal of background medication, with 37 (63.8%) as mono- and 21 (36.2%) as polytherapy. Among all subjects, 32 (55.2%) were free from seizure occurrence under lacosamide monotherapy throughout the 12-month follow-up; a reduction of seizure frequency ≥75% compared to the 1-year before employment of lacosamide occurred in the remaining five (8.6%) subjects taking lacosamide as single agent. The maintenance dosage of lacosamide as monotherapy was 400 (IQR 350–400) mg/day.

A post hoc analysis of the historical-controlled conversion to lacosamide monotherapy study was conducted by Wechsler, et al[25]. This trial served as the pivotal trial for the monotherapy indication granted by the FDA. In this trial a total of 425 patients were enrolled with 383 patients completing the titration phase of the trial which used lacosamide 300mg/day or 400mg/day in the randomization arms. They reported that seizure freedom and reduction of seizure frequency greater than 50% compared to baseline occurred in near to 15% and in the 60% of the subjects completing the monotherapy phase, respectively. This study differed from the report by Lattanazi in that a high proportion of patients somewhat more drug resistant than would usually be considered for monotherapy in clinical practice, characterized by high baseline seizure frequency, history of three or more lifetime AEDs or concomitant treatment with more than one AED, and for the conversion to single-drug regimen despite the response obtained throughout the maintenance phase.

In a open-label, multicenter trial, patients with partial onset seizures were initiated on oral lacosamide (titrated to 400 mg/day) and defined as belonging to either add-on therapy to first AED monotherapy, or as later add-on therapy to 1–3 concomitant AEDs after ≥2 previous AEDs.[26] The primary efficacy variable was the proportion of patients achieving seizure freedom for the first 12 weeks of the 24-week maintenance phase. In the first add-on cohort, 27/72 (37.5%) patients completed 12 weeks treatment and remained seizure-free; 18/68 (26.5%) remained seizure-free after 24 weeks. 64/91 (70.3%) patients achieved ≥50% reduction in seizure frequency during maintenance treatment.

Conclusion

Lacosamide possesses several characteristics which make it an optimal choice in the treatment of seizures. It has a unique mechanism of action, selectively enhancing slow inactivation of voltage-gated sodium channels. Its mechanism of action could be exploited to reduce the percentage of pharmacoresistant patients. Lacosamide is rapidly and completely absorbed following oral administration, with negligible first-pass effect. There is dose equivalence for all the formulations of lacosamide, oral tablet, oral solution and intravenous solution. This enables patients to convert between formulations based on clinical situations. This is especially important in the transition from intravenous requirements during SE to maintenance therapy with an oral agent after the acute period. Additionally, lacosamide does not require prolonged infusions such as phenytoin does due to cardiac and hypotension concerns. Lacosamide has an elimination half-life of approximately 13 h, allowing for less frequent dosing and appears to have no appreciable pharmacokinetic drug interactions.

In the treatment of SE lacosamide has demonstrated level II-2 efficacy in the treatment of RSE and NCSE based on a retrospective comparator cohort (Level II-2 articles are defined as cohort or case–control studies). Level III evidence has been demonstrated in prospective non-comparative studies and retrospective non-comparative case series (Level III studies are defined as descriptive studies and case reports). A pilot study has demonstrated the efficacy of lacosamide in the treatment of NCSE post stroke in elderly patients.

Lacosamide monotherapy has demonstrated efficacy in both treatment naïve patients and patients receiving lacosamide as adjunct therapy with conversion to lacosamide monotherapy. This is paired with a favorable safety profile in this patient population. Lacosamide demonstrates a positive impact on clinically relevant measures, and is a well-tolerated alternative for conversion to monotherapy in patients with uncontrolled focal epilepsy.

Table 1 Management of refractory status epilepticus.

Trial	Design (LOE)	*N*	Patient characteristics	Seizure types	Other AEDs	Lacosamide regimen	Outcomes
Sutter et al. (2013)	Retrospective comparative cohort (II-2)	111	Male 54% Mean age: 62 ± 16 y	Focal or absence SE 26% NCSE 65% GCSE 9%	BDZ plus PHT and/or VPA and/or LEV Then IV anesthetic or other AED after failure of first- and second-line agents Mean failed AEDs: 3 ± 0.9 (range 1–5)	200 mg IV BID Dose reductions for renal dysfunction One dose escalation to 600 mg/day for obesity (>110 kg) vs. Any other agents	86 analyzed for comparison Duration of SE (mean ± SD) No LCM: 134.3 ± 188.7 h LCM: 87.2 ± 159.4 h (NSS) Seizure control No LCM: 85% LCM: 93% (NSS) Death No LCM: 39% LCM: 20% (OR 0.34, 95% CI 0.1–0.9)
Kellinghaus et al. (2014)	Retrospective comparative cohort (II-2)	46	Male 50% Median age: 68 (18–90) y	Focal SE 41% NCSE 33% GCSE 26% Median interval from SE onset to therapy: 0.75 h (range 0.2–336 h)	BDZ plus LEV	200–800 mg IV (median 400 mg) vs. PHT 750–1500 mg (median 1500 mg) vs. Any other AED	36 analyzed for comparison of LCM vs. PHT Seizure termination after administration: LCM: 7/21 (33%) PHT: 6/15 (40%) (*p* = 0.68) Time to seizure termination (median): LCM: 9.5 h (0.5–240 h) PHT: 13.5 h (0.5–28.5 h) (*p* = 0.48)
Miro et al. (2013)	Prospective, descriptive (III)	34	Male 53% Mean age: 60 y (22–86)	FMSE 82.4% NCSE 14.7% GCSE 2.8%	BDZ plus PHT and/or VPA and/or	100–400 mg IV bolus (at median of 48 h (range 1–250 h) after SE therapy	Seizure termination with no further AED change × 48 h: 64.7%

				Median interval from SE onset to therapy: 4.5 h (range 0.3–240 h)	LEV Failed ≥4 AEDs: 76.5%	initiated) 100 mg IV (2.9%) 200 mg IV (20.6%) 300 mg IV (26.5%) 400 mg IV (50%) Maintenance: 100–600 mg po or IV/day (mean 323.53 mg) (LCM used as a 4th or later option in 76.5% of patients)	
Legros et al. (2014)	Prospective, descriptive (III)	25	Male 52%	RSE 84% SC 16% Mix of convulsive, non-convulsive, generalized, partial	Number of AEDs failed (median 3; range 1–5) BDZ then PHT and/or VPA and/or LEV Then IV anesthetic or other AED	200 mg IV over 15 min vs. 400 mg IV over 15 min Subsequent dose 200 mg po q12 h	Seizure cessation after administration: Overall: 36% (9/25) 200 mg: 18.2% (2/11) 400 mg: 50% (7/14) (p = 0.2) Seizure termination within 3 h: 200 mg: 0% (0/11) 400 mg: 28.6% (4/14) (p = 0.023)
Albers et al. (2011)	Retrospective, descriptive (III)	7	Male 86% Age range: 33–83 y	Focal 71% GCSE 29%	Prior BDZ, LEV, PHT, VPA, TPM, anesthetic Order of IV LCM 2nd: 14% 4th: 29% 5th: 57%	Loading dose 400 mg IV Maintenance 400 mg/d IV	Seizure cessation within 24 h with no additional AEDs required: 100%
Goodwin et al. (2011)	Retrospective, descriptive (III)	9	Male 22% Age range: 47–89 y	NCSE 67% GCSE 33% Median interval from SE onset to LCM	Failure of 2 AEDs or more (median 3; range 2–5) Other AED: BDZ, PHT,	Loading dose 100–300 mg IV Maintenance dose 100–200 mg IV BID (max 200	Seizure cessation within 4 h or absence of EEG seizure activity for 24 h following emergence from burst

				therapy: 2 d (range 0–14 d)	LEV PB	mg IV q8 h)	suppression: 0/9 (0%)
Höfler et al. (2011)	Retrospective, descriptive (III)	31	Male 55% Median age: 67 y (22–95)	FMSE 32% NCSE 32% GCSE 36%	BDZ or PHT or VPA or LEV or anesthetic Order of IV LCM 1st: 6.5% 2nd: 19.4% 3rd: 48.4% 4th: 25.8%	200–400 mg IV (median 200 mg) at max rate 60 mg/min Subsequent dose 0–400 mg IV (median 200 mg)	SE cessation after administration: 80.6% (25/31) Order of IV LCM 1st: 100% (2/2) 2nd: 100% (6/6) 3rd: 73% (11/15) 4th: 75% (6/8)
Kellinghaus et al. (2011)	Retrospective, descriptive (III)	39	Male 46% Mean age: 63 y (18–90)	Focal 85% GCSE 15% Median interval from SE onset to therapy: 0.75 h (range 0.1–336 h)	1st line BDZ: 95% Prior LEV: 85% PHT: 36% Other AED: 13% Anesthetic: 10% Order of IV LCM 1st: 3% 2nd: 10% 3rd: 49% 4th or greater: 38%	200–400 mg IV bolus over ≤ 5 min	SE cessation after administration: 44% (17/39) Order of IV LCM 1st or 2nd: 60% (3/5) 3rd: 57% (11/19) 4th or greater: 20% (3/15)
Koubeissi et al. (2011)	Retrospective, descriptive (III)	4	Male 0% Age range: 53–79 y	NCSE 100% Interval from SE onset to LCM therapy: range 3–50 h	Failure of BDZ and one or more of PHT, LEV and pregabalin Order of IV LCM 3rd: 50% 5th: 50%	Loading dose 50–100 mg IV Maintenance 100–200 mg IV BID	Seizure cessation: 100% Time from LCM administration to seizure cessation: 15 min–2 h
Rantsch et al. (2011)	Retrospective, descriptive (III)	10 episodes in 9 patients	Male 33% Mean age: 67.1 ± 12.4 y	NCSE 80% Focal 20% Median interval from SE onset to LCM therapy: 166 h (range 8–637 h)	Lacosamide 4th line or greater (median 6.5, range 4–12)	Loading dose 50–100 mg IV Maintenance dose 50 mg IV BID	Seizure cessation after administration: 2/10 (20%)

Cherry et al. (2012)	Retrospective, descriptive (III)	13 episodes in 10 patients	Male 38% Mean age: 51.1 y (24–80)	FMSE 33% NCSE 48% GCSE 7.5% Myoclonic 7.5%	Failure of 2 AEDs (mean 2.8; range 1–7) BDZ, LEV, PHT, VPA, PB, other AED, anesthetic	Loading dose Mean 178 mg (50–400 mg) at mean 3.1 mg/min (range 1.7–6.7 mg/min) Maintenance dose Mean 326 mg/d (100–400 mg/d)	Seizure cessation after administration: 38% (5/13) Time to seizure cessation: 11.2 h (range 1.5–21 h) >50% reduction in seizure: 54% (7/13)
Mnatsakanyan et al. (2012)	Retrospective, descriptive (III)	10	Male 40% Age: 16–90 y	NCSE 100%	Failure of "standard treatment" including BDZ Other AED: PHT, LEV, VPA, PB, anesthetic, TPM, LTG	Loading dose 200–300 mg IV over ≤ 30 min Maintenance dose 200–400 mg/d	Seizure cessation after administration: 70% (7/10)
Garces et al. (2014)	Retrospective, descriptive (III)	55	Male 38% Mean age: 65.1 y (18–90)	NCSE 78.2% GCSE 9.1% FMSE 12.7%	Prior BDZ 51% LEV: 85% PHT: 25% VPA: 18% Other AED: 7% Anesthetic: 4% Order of IV LCM 1st: 1.8% 2nd: 40% 3rd: 34.5% 4th or greater: 23.6%		

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Appendix:

Appendix A

Clinical Effiacy of Lacosamide for Partial-Onset Seizures					
Investigators/ Design	**Eligibility Criteria**	**Interventions/ N**	**Primary Efficacy Endpoint**	**Efficacy Results**	**Safety**
Chung S. *etal* (2010) 20-week DB, MC, PC, RCT, ITT	Uncontrolled partial-onset seizures taking 1-3 AEDs Age: 16-70	Tx1: Lacosamide 400mg Tx2: Lacosamide 600mg N=405	Median percent reductions in seizure frequency per 28 days	Tx1: 37.3% (p=0.008) Tx2: 37.8% (p=0.006)	AEs occurring in ≥5%: Dose-related dizziness, nausea, diplopia, blurred vision, HA, tremor, and vomiting
			Responder Rate	Tx1: 38.3% (p<0.001) Tx2: 41.2% (p<0.001)	
Halasz P. *etal* (2009) 24-week DB, MC, PC, RCT, ITT	Uncontrolled partial-onset seizures taking 1-3 AEDs Age: 16-70	Tx1: Lacosamide 200mg Tx2: Lacosamide 400mg N=485	Median percent reductions in seizure frequency per 28 days	Placebo: 20.5% Tx1: 35.3% (p=0.02) Tx2: 36.4% (p=0.03)	AEs occurring in ≥5%: Dizziness, HA, diplopia, nausea, vertigo, fatigue, naso- pharyngitis, coordination abnormality, and vomiting. Overall 8.7% discontinued due to treatment AEs
			Responder Rate	Placebo: 25.8% Tx1: 35.0% (p=0.07) Tx2: 40.5% (p=0.01)	
Ben-Menachem *etal.* (2007) 24-week DB, MC, PC, RCT, ITT	Uncontrolled partial-onset seizures taking 1-2 AEDs Age: 18-65	Tx1: Lacosamide 200mg Tx2: Lacosamide 400mg Tx3: Lacosamide 600mg N=418	Median percent reductions in seizure frequency per 28 days	Placebo: 10% Tx1: 26% (p=0.1010) Tx2: 39% (p=0.0023) Tx3: 40% (p=0.0084)	84% of pts experienced at least on tx emergent AE. AE occurring ≥10%: dizziness, HA, nausea, fatigue, ataxia, vision abnormality, vomiting, diplopia, somnolence and nystagmus
			Responder Rate	Placebo: 21.9% Tx1: 32.7% (p=0.0899) Tx2: 41.1% (p=0.0038) Tx3: 38.1% (p=0.0141)	
DB: Double Blind MC: Multi-centered PC: Placebo Controlled RCT: Randomized Controlled Trial ITT: Intention to treat AED: Anti-epileptic Drug HA: headache					