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Lacosamide

In Partial-Onset Seizures

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Contents

Abstract

▲ Lacosamide is a functionalized amino acid, the antiepileptic effects of which appear to be due to a novel mode of action, namely the selective enhancement of slow inactivation of voltage-gated sodium channels.

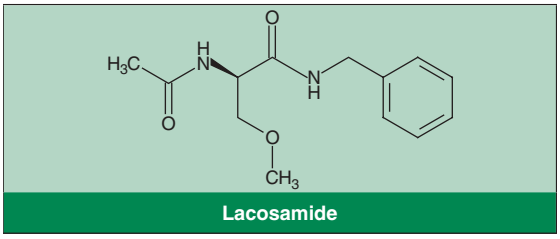
▲ Lacosamide is available as oral or intravenous formulations. Bioequivalence between the oral tablet and the oral syrup of lacosamide has been established. The bioavailability of the oral lacosamide tablet was similar to that of a 30- or 60-minute intravenous infusion of lacosamide administered at the same dosage.

▲ Oral lacosamide when added concomitantly with between one and three antiepileptic drugs was effective in adult patients with uncontrolled partial-onset seizures with or without secondary generalization, according to pooled data (n = 1308) from three phase II/III studies that had a 12-week maintenance phase. The percentage of patients with a ≥50% reduction from baseline to the maintenance phase in seizure frequency was significantly greater with oral lacosamide 200 or 400 mg/day (34% and 40%) than with placebo (23%).

▲ The median percentage reduction in seizure frequency per 28 days from baseline to the maintenance phase was significantly greater with lacosamide 400 mg/day than with placebo in each of the three phase II/III studies.

▲ Lacosamide was generally well tolerated in adult patients with partial-onset seizures, with most treatment-emergent adverse events being of mild or moderate severity. Dizziness was the most common treatment-related adverse event. When used as short-term replacement for oral lacosamide, intravenous lacosamide was well tolerated when administered as a 15-, 30- or 60-minute infusion.

Features and properties of lacosamide (Vimpat®)	
Indication	
Adjunctive therapy in the treatment of partial-onset seizures in adult patients with epilepsy	
Proposed mechanism of action	
Selective enhancement of slow inactivation of voltage-gated sodium channels	
Dosage and administration	
Starting dosage	100 mg/day
Maintenance dosage	200–400 mg/day
Frequency of administration	Twice daily
Route	Oral or intravenous
Pharmacokinetic profile (a single oral dose of lacosamide 400 mg in healthy male volunteers)	
Area under the plasma concentration-time curve	143 μg • h/mL
Maximum plasma concentration (C_{max})	8.7 μg/mL
Time to C_{max}	≈1–4 hours
Elimination half-life	≈13 hours
Bioavailability	≈100%
Protein binding	<15%
Most common treatment-emergent adverse events (reported in ≥10% of patients)	
Dizziness, headache, nausea and diplopia	



Epilepsy, a neurological disorder characterized by recurrent unprovoked seizures, has an estimated annual incidence of ≈50 per 100 000 people/year in developed countries.[1] Epilepsy is not a uniform condition and is comprised of many different seizure types and epilepsy syndromes.[1] Seizures can be broadly categorized into two types: partial-onset (which may become secondarily generalized) and generalized. However, some patients have seizures that cannot be classified into either of these two groups. Abnormal epileptic firing of cells in a localized area(s) of the brain results in partial-onset seizures. These may manifest as motor, somatosensory, autonomic, other sensory or psychic symptoms with undisturbed (simple partial seizures) or lost or altered consciousness (complex partial seizures).[2] If epileptic activity spreads to the entire brain, a secondarily generalized seizure may develop.[2] In adults, more than half of all seizures are partial-onset seizures.[1]

A wide range of antiepileptic drugs (AEDs) are available for the treatment of partial-onset seizures;[3,4] however, seizures persist despite treatment in ≈35% of patients with partial epilepsy.[5]

Lacosamide (Vimpat®) the *R*-enantiomer of 2-acetamido-N-benzyl-3-methoxypropionamide, is a functionalized amino acid and is available as oral and intravenous formulations.[6-8] Lacosamide is approved in the EU[6] and the US[9] for use as adjunctive therapy in the treatment of partial-onset seizures (with or without secondary generalization[9] [EU]) in patients with epilepsy (aged ≥16 [EU][6] or ≥17[9] [US] years). This profile reviews the pharmacological and clinical profile of oral and intravenous lacosamide in this indication.

Medical literature referenced in this profile was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles.

1. Pharmacodynamic Profile

Mechanism of Action

- The precise mechanism by which lacosamide exerts its antiepileptic effect in humans has not been established; however, a novel mode of action has been proposed.[10]
- In *in vitro* electrophysiological studies, lacosamide selectively enhanced slow inactivation of voltage-gated sodium channels, without affecting the fast inactivation mechanism.[11] This resulted in the stabilization of hyper-excitable physiological neuronal membranes and the inhibition of repetitive neuronal firing without affecting physiological neuronal excitability.[7]
- *In vitro* studies suggest that lacosamide may interact with the collapsin response mediator protein-2.[10,11] This protein is dysregulated in the brain of epileptic patients.[12]
- Lacosamide 10–100 μmol/L did not bind with high affinity (<50% inhibition of radioligand binding) to a wide range of animal or recombinant human receptor sites (including those for NMDA, benzodiazepine, GABA, adenosine, cannabinoids, dopamine, histamine, serotonin, muscarine) or ion channels (N- and L-type voltage-gated calcium, adenosine triphosphate-sensitive potassium, voltage-gated potassium and chloride channels).[10,13,14]
- Lacosamide 10 μmol/L did not inhibit the uptake of norepinephrine, dopamine, serotonin or GABA, and lacosamide 10–100 μmol/L did not inhibit GABA transaminase.[14]

Effects in Animal Models of Epilepsy

- Lacosamide protected against seizures in a broad range of animal models of partial and primary generalized seizures, and delayed kindling development.[10,15]

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- Intraperitoneal lacosamide provided protection against audiogenic seizures in the Frings mouse model, with a median effective dose (ED_{50}) of 0.63 mg/kg.[10]
- Lacosamide provided protection in animal models against tonic-clonic seizures induced by maximal electroconvulsive shock, demonstrating that this agent inhibits seizure spread.[10]
- In the 6-Hz psychomotor seizure test (a model for seizures resistant to treatment), intraperitoneal lacosamide was effective in preventing seizures (ED_{50} 9.99 mg/kg).[10,15]
- Intraperitoneal lacosamide elevated the seizure threshold in the intravenous pentylenetetrazole seizure test in rodents. However, lacosamide was ineffective against clonic seizures induced by a subcutaneous bolus injection of pentylenetetrazole (EC_{50} >25 mg/kg), the $GABA_A$-receptor bicuculline (EC_{50} >50 mg/kg) or the chloride-channel blocker picrotoxin (EC_{50} >30 mg/kg) in rodents.[10,15]
- Intraperitoneal lacosamide 20 and 50 mg/kg completely prevented tonic convulsions, with lacosamide 50 mg/kg providing partial (50%) protection against clonic convulsions induced by NMDA in mice.[15]
- Intraperitoneal lacosamide was effective in the hippocampal kindling rat model (thought to reproduce complex partial seizures), reducing seizure score and after discharge duration in a dose-dependent manner (ED_{50} 13.5 mg/kg).[15] In this model, lacosamide (25 mg/kg) was superior to maximally effective doses of phenytoin (150 mg/kg), carbamazepine (50 mg/kg), valproate (250 mg/kg) and ethosuximide (250 mg/kg) in decreasing after-discharge duration by >85%.[10]
- Lacosamide was effective in models of *status epilepticus*, stopping limbic seizures induced by self-sustaining status epilepticus in rats within 15 minutes of administration and preventing their recurrence over the next 24 hours. Histological examination of dorsal hippocampus brain of lacosamide-treated rats revealed less damage in sections of this tissue than in those from control animals, suggesting a neuroprotective effect of lacosamide.[10]
- In preclinical models of epilepsy, lacosamide demonstrated additive or synergistic effects when combined with a variety of AEDs, including levetiracetam and carbamazepine.[10]

Effects on Cardiac Parameters

- Lacosamide was not associated with a prolongation of the rate-corrected QT interval and did not have any dose-related or clinically important effect on QRS duration, according to data from a randomized, double-blind, thorough QT study[16] in 247 healthy volunteers treated with lacosamide 400 or 800 mg/day for 6 days.[9,17]
- Lacosamide was associated with dose-related increases in the PR interval. In the thorough QT study, the maximum mean changes in PR interval at steady state (day 6) occurred 1 hour after drug administration and were 6.3, 13.6 and 18.2 ms in the placebo, lacosamide 400 and 800 mg/day groups, respectively.[9,17,18] In the placebo-controlled studies in patients with partial-onset seizures (see section 3), the placebo-subtracted mean maximum increase in PR interval was 3.1 ms with lacosamide 400 mg/day.[9]

2. Pharmacokinetic Profile

- Following oral administration, lacosamide undergoes rapid and complete absorption, with negligible first-past effect and with an oral bioavailability of ≈100% in healthy volunteers.[6,9,19] The rate and extent of absorption are not affected by the presence of food.[19,20]
- After administration of a single oral dose of lacosamide 400 mg in a dose-escalating study in 16 healthy male volunteers,[21] the peak plasma concentration (C_{max}) of unchanged lacosamide was reached after ≈1–4 hours.[6,9,21] The C_{max} was 8.7 μg/mL and area under the plasma concentration-time curve (AUC) was 143 μg • h/mL
- The lacosamide C_{max} was reached at the end of infusion when administered intravenously.[6,9]
- The pharmacokinetics of both oral and intravenous lacosamide were dose-proportional (over the dose range of 100–800 mg), with low intra- and inter-subject variability.[6,9] Following twice-daily

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administration of oral lacosamide, steady-state plasma concentrations were reached after 3 days.

- Mean lacosamide plasma concentrations at the end of a 12-week, maintenance phase in 418 patients with partial-onset seizures in a randomized, double-blind, multicentre study (see section 3 for further study design details) were 4.99 μg/mL with lacosamide 200 mg/day and 9.35 μg/mL with lacosamide 400 mg/day.[22]
- Bioequivalence between the tablet and the syrup formulations of lacosamide (both for oral administration) has been established.[6]
- The bioavailability of lacosamide when administered as an oral tablet (200–600 mg/day) was similar to that when administered as a 30- or 60-minute infusion at the same dosage.[9,23] In a randomized, double-blind study in 59 patients with partial-onset seizures, the AUC of the intravenous lacosamide AUC was ≈100% that of the oral lacosamide (assessed on day 2 of administration).[23]
- Lacosamide plasma protein binding is <15%.[6,9,19] The volume of distribution of lacosamide is ≈0.6 L/kg.[6,9]
- Elimination of lacosamide from the systemic circulation is primarily via urinary excretion and biotransformation.[6,9] After oral and intravenous administration of radiolabeled lacosamide, ≈95% of the radioactivity was recovered in the urine and <0.5% in the faeces.[6,9,19] Lacosamide was eliminated in the urine unchanged (≈40% of the administered dose) and as the *O*-desmethyl metabolite (<30%). A polar fraction (possibly serine derivatives) accounted for ≈20% of the radioactivity in the urine. This derivative is found in small amounts (0–2%) in the plasma of some patients. Additional metabolites were also found in small amounts (0.5–2%) in the urine.
- The elimination half-life of unchanged lacosamide was ≈13 hours.[6,9,19]
- The pathway for the metabolism of lacosamide has not been completely characterized.[6,9] The cytochrome P450 (CYP) isoenzyme 2C19 is mainly responsible for the formation of the *O*-desmethyl metabolite. However, there were no clinically relevant differences in the pharmacokinetics of lacosamide when it was administered to extensive metabolizers (with a functional CYP2C19) versus poor metabolizers (lacking functional CYP2C19). Moreover, omeprazole (a CYP2C19-inhibitor) did not have any clinically relevant effect on the pharmacokinetics of lacosamide, indicating that the metabolic pathway involving CYP2C19 is minor. No other enzymes involved in the metabolism of lacosamide have yet been identified.
- The plasma concentrations of lacosamide were similar in male and female recipients of this agent.[6,9,24]
- The lacosamide AUC in 11 elderly men (aged >65 years) was ≈30% greater than that in 12 younger men (aged 18–45 years); the lacosamide AUC in 12 older women (aged >65 years) was ≈12% greater than that in 31 younger women (aged 18–45 years), and is partly a result of the lower body water in the elderly.[24] The renal clearance of lacosamide was only slightly reduced in elderly subjects. Dose reductions are not required in the elderly, unless these patients have renal impairment.[6]
- Compared with the AUC of lacosamide in subjects with normal renal function (creatinine clearance [CL_{CR}] >80 mL/min), the AUC of subjects with mild (CL_{CR} 50–80 mL/min) or moderate (CL_{CR} 30–50 mL/min) renal impairment was increased ≈25% and that in patients with severe renal impairment (CL_{CR} ≤30 mL/min) was increased 60%; the lacosamide C_{max} remained unchanged in all subjects.[6,9] No dosage adjustment was considered necessary in patients with mild or moderate renal impairment.[6,9] In patients with severe renal impairment and those with end-stage renal disease, a maximum dosage of 250 (EU[6]) or 300 (US[9]) mg/day is recommended. Lacosamide is removed from the plasma by haemodialysis; therefore, dosage supplementation of up to 50% is recommended following haemodialysis.[6,9]
- The AUC of lacosamide in patients with moderate hepatic impairment (Child-Pugh B) was ≈50–60% higher than that in healthy subjects.[6,9] However, it was estimated that the increased AUC was partly due (19%) to the reduced renal function of these patients.[9] Caution in the titration of

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lacosamide is advised in patients with mild to moderate hepatic impairment.[6,9] The pharmacokinetics of lacosamide have not been investigated in patients with severe hepatic impairment and the use of lacosamide in this patient population is not recommended.[6,9]

- *In vitro* studies suggest that lacosamide has a low potential for interactions with other drugs. The enzymes CYP1A2, 2B6, 2C9, 2C19 and 3A4 were not induced and CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1 and 3A4/5 were not inhibited by lacosamide at clinically relevant plasma concentrations.[6,9,10] During *in vivo* studies, the enzyme CYP2C19 was not induced or inhibited by lacosamide.[10]
- Drug interaction studies indicated that lacosamide did not affect the pharmacokinetics of valproic acid,[6,9,25] carbamazepine,[6,9,25] metformin,[6,9,26] digoxin[6,9,27] or omeprazole.[6,9] Lacosamide did not affect the pharmacokinetics of the oral contraceptives ethinylestradiol and levonorgestrel.[6,9,27] Progesterone concentrations were not affected by the coadministration of lacosamide and the oral contraceptives.
- The AEDs valproic acid and carbamazepine had no influence on the pharmacokinetics of lacosamide 400 mg/day.[6] The AUC of lacosamide was increased by 19% when coadministered with omeprazole 40 mg once daily; however this effect was not considered to be clinically relevant.[6] Plasma levels of the O-desmethyl metabolite were reduced by ≈60% when lacosamide was coadministered with omeprazole.[9]
- During the clinical studies discussed in section 3,[22,28,29] lacosamide did not alter the mean plasma concentrations of concomitantly administered AEDs, including carbamazepine, the monohydroxy derivative of oxcarbazepine, lamotrigine, levetiracetam, phenytoin, topiramate or valproic acid. However, a population pharmacokinetic analysis of these studies indicated that concomitant administration of lacosamide and AEDs that were enzyme inducers (e.g. carbamazepine, phenytoin, phenobarbital) reduced the overall systemic exposure of lacosamide by 15–25%.[6,9]

3. Therapeutic Efficacy

Phase II/III Studies

The therapeutic efficacy of adjunctive oral lacosamide in adult patients with partial-onset seizures has been evaluated in three large (n > 400), phase II/III, randomized, double-blind, placebo-controlled, multicentre studies.[22,28,29] One study is currently only available as an abstract.[29] Data have also been obtained from the European Public Assessment Report (EPAR) for lacosamide,[18] the US manufacturer's prescribing information[9] and the EU summary of product characteristics (SPC).[6]

This section will focus on efficacy data involving the approved lacosamide dosage of 200 or 400 mg/day.

Patients eligible for enrolment in the studies were aged 16–70 years,[22,28,29] with a diagnosis of simple and/or complex partial-onset seizures (based on the International Classification of Epileptic Seizures [1981]),[30] with or without secondary generalization. Patients had partial-onset seizures for at least the last 2 years despite prior treatment with at least two AEDs.[18,22] Overall, nearly half of the patients had been treated with seven or more AEDs in their lifetime.[18]

Exclusion criteria included previous treatment with lacosamide, a history of chronic alcohol or drug abuse, non-epileptic or psychogenic seizures, seizures that were uncountable due to clustering, primary generalized seizures, status epilepticus in the previous 12 months, or a known history of severe anaphylactic reactions or serious blood dyscrasias.[18,22,28,29]

The three studies consisted of four phases: baseline, titration, maintenance and transition/taper.[22,28,29]

After enrolment, patients entered an 8-week baseline phase, during which they had to have an average of four or more partial-onset seizures per 28 days with a seizure-free period no longer than 21 days.[9,18,22,28,29]

Patients were also receiving one to two[22] or one to three[28,29] concomitant AEDs, with or without

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current vagus nerve stimulation, for the 4 weeks prior to enrolment, throughout the baseline period and for the remainder of the study. The dosages of concomitant AEDs remained stable throughout the study.

After the 8-week baseline period, eligible patients were randomized to a double-blind treatment phase involving a 4-[28] or 6-[22,29] week, forced dose-titration period, up to the respective randomized dosage of 100,[22,28] 200[22,28,29] or 300[22,29] mg twice daily. Lacosamide was initiated at 100 mg/day and increased in weekly increments of 100 mg/day.[22,28,29] Patients experiencing intolerable adverse events were allowed one down-titration of 100 mg/day at the end of the titration period. Patients then entered a 12-week maintenance phase, during which patients remained on a stable dosage of lacosamide,[22,28,29] followed by a 2-week transition (if entering an open-label extension study) or a 2-[28] or 3- week[22,29] taper phase (if not entering the open-label extension phase).

Across the three studies, a total of 1308 patients with a mean duration of epilepsy of 23.7 years were randomized to the double-blind treatment phase.[9,18] Most patients (84%) were taking two or three concomitant AEDs with or without vagal nerve stimulation.[9] The median baseline seizure frequency for patients included in the efficacy analysis (n = 1294) was 9.9–16.5 seizures per 28 days.

The primary efficacy endpoint for the European regulatory authorities was the 50% responder rate (defined as the percent of patients with a ≥50% reduction in seizure frequency from baseline to the maintenance phase).[18] The primary endpoint for the US FDA was the change in partial seizure frequency per 28 days from baseline to the maintenance phase.[18,22,28,29]

The primary analyses were based on the intent-to-treat (ITT) population,[22,28,29] and included all randomized patients who received one or more doses of study medication and had one or more post-baseline efficacy assessments. The per-protocol (PP) analysis included all patients in the ITT population who had at least one efficacy assessment during the maintenance phase and who did not have any major protocol violations.

- Adjunctive treatment with oral lacosamide, compared with placebo, was associated with a greater proportion of patients responding to treatment. According to a pooled analysis of the three phase II/III studies,[6,9,18] the 50% responder rate was 23%, 34% and 40% for placebo, lacosamide 200 mg/day and lacosamide 400 mg/day.
- The 50% responder rates for the ITT and PP populations for each of the individual studies are shown in figure 1. According to the ITT analysis, there was no significant difference in the responder rate for lacosamide 200 mg/day versus placebo in the two studies that assessed this lacosamide dosage;[22,28] however, according to the PP analysis, there was a significant between-group difference for one of these studies (figure 1).[22]
- The median percentage reduction in partial seizure frequency per 28 days from baseline to the maintenance phase was significantly greater with lacosamide 400 mg/day than with placebo in the ITT population in each of the three studies (figure 1).[22,28,29] There was a significant difference in this parameter between lacosamide 200 mg/day and placebo in the ITT population in one[28] of the two[22,28] studies that administered this lacosamide dosage (see figure 1). According to the PP analysis, the difference between lacosamide 200 mg/day and placebo was significant in both studies (see figure 1).[22,28]

Open-Label Extension Studies

Three ongoing open-label extension trials of the phase II/III studies are investigating the long-term efficacy of adjunctive lacosamide in patients with partial seizures.[18,31-33] An interim analysis of one of these studies in which patients received lacosamide for up to 5.5 years is available (presented in an abstract).[34] Among the 370 patients who enrolled in the extension study, 76.8% of patients had received lacosamide for >12 months, 60.5% had received lacosamide for >24 months and 37.8% of patients had received lacosamide for >36 months.

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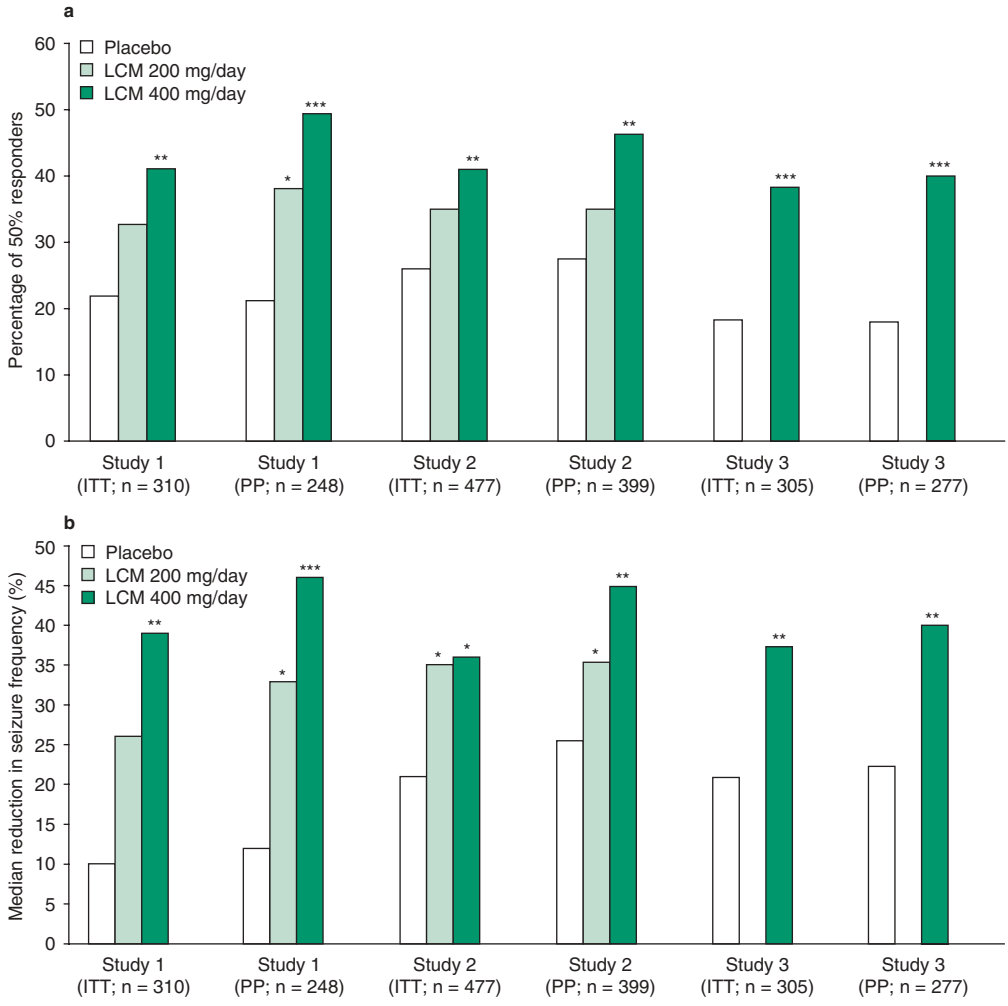

Fig. 1. Efficacy of oral lacosamide (LCM) as adjunctive treatment in adult patients with partial-onset seizures in randomized, double-blind, placebo-controlled, multicentre studies (study 1,[22] study 2[28] and study 3[29]). Only data relating to the recommended LCM dosages of 200 and 400 mg/day are presented (ITT; n = 1092 and PP; n = 924). Following an 8-week baseline phase, patients were randomized to LCM 100,[22,28] 200[22,28,29] or 300[22,29] mg twice daily or placebo. Treatment was initially titrated over a 4-[28] or 6-[22,29] week period and then continued in a 12-week maintenance phase. Patients continued with concomitant antiepileptic drugs with or without vagus nerve stimulation. (**a**) Percentage of patients with a ≥50% reduction in seizure frequency from baseline to the maintenance phase (50% responder rate); p-values are based on pairwise-treatment logistic-regression models. (**b**) Median percent reduction in seizure frequency per 28 days from baseline to the maintenance phase; p-values are based on log-transformed data from pairwise treatment ANCOVA models; **ITT** = intent-to-treat; **PP** = per protocol; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs placebo.

The median modal lacosamide dosage was 400 mg/day.[34]

- Lacosamide demonstrated long-term efficacy as adjunctive treatment in patients with partial-onset seizures. According to the interim analysis of this ongoing extension study,[34] the median percentage reduction in seizure frequency per 28 days during the open-label phase from baseline (established in the previous trial) was 45.9%; the 50% responder rate was 46.6%.

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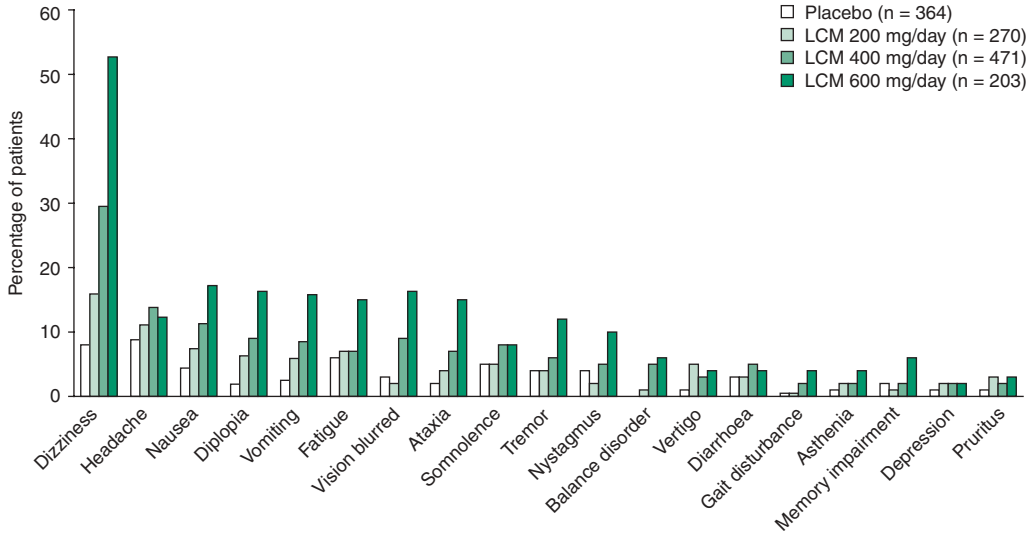

Fig. 2. Tolerability of oral lacosamide (LCM) in 1308 patients with uncontrolled partial-onset seizures. Treatment-emergent adverse events reported in ≥2% of recipients of oral LCM and more frequently than in placebo recipients during the 4-[28] or 6-[22,29] week forced dose-titration period and a 12-week maintenance phase, according to a pooled analysis (reported in the US prescribing information[9]) of data from three phase II/III, randomized, double-blind, placebo-controlled, multicentre studies (see section 3 for further study design details). Patients received LCM 100, 200 or 300 mg twice daily or placebo in addition to 1–2 antiepileptic drugs with or without vagus nerve stimulation.

4. Tolerability

This section focuses largely on pooled tolerability data (presented in the EU lacosamide EPAR[18] and SPC[6] and the US manufacturer's prescribing information[9]) from the three phase II/III studies (see section 3 for further study design details) in which a total of 1308 patients with partial-onset seizures received oral lacosamide 200–600 mg/day or placebo.

- Lacosamide was generally well tolerated in patients with partial-onset seizures, with most treatment-emergent adverse events being of mild or moderate severity.[6,9] The overall incidences of treatment-emergent adverse events occurring during the treatment phase (titration plus maintenance) were 65% in placebo recipients and 70% and 82% in recipients of the recommended dosages of lacosamide 200 and 400 mg/day.[35]
- The most common treatment-emergent adverse events in recipients of oral lacosamide involved the nervous or gastrointestinal systems, and included dizziness, headache, nausea and diplopia.[6,9,18] Other treatment-emergent adverse events reported in ≥2% of lacosamide recipients and more frequently than in placebo recipients are shown in figure 2. Overall, the incidence of nervous system (especially dizziness) and gastrointestinal adverse events were dose related.[6,18]
- Discontinuation due to an adverse event occurred in 8% and 17% of recipients of lacosamide 200 and 400 mg/day (recommended dosage), 29% of recipients of lacosamide 600 mg/day (nonapproved dosage) and 5% of placebo recipients.[9] The most common adverse events (>1% of lacosamide recipients and greater than placebo) leading to discontinuation were dizziness, ataxia, vomiting, diplopia, nausea, vertigo and blurred vision.
- The nature of treatment-emergent adverse events associated with long-term (up to 5.5 years) oral lacosamide, according to the interim analysis of an open-label extension study (section 3) was generally similar to that reported in the initial phase II/III studies.[34] Adverse events resulted in discontinuation in 11.1% of lacosamide recipients.
- Lacosamide was associated with small dose-dependent prolongations in the PR interval (see section 1), with a consequent risk for atrio-ventricular (AV)

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blockade.[6] In clinical studies in patients with partial onset-onset epilepsy, the incidence of first-degree AV block was 0.4% in the 944 patients randomized to lacosamide and 0% in the 364 patients randomized to placebo.[9] There were no reports of second- or third-degree AV block.[6]

- Syncope was not commonly reported in epilepsy patients, occurring in 0.1% of lacosamide recipients and 0.3% of placebo recipients.[6]
- Abnormal liver function tests have been reported in the phase II/III studies in patients with partial-onset seizures. According to the US prescribing information,[9] elevations of ALT greater than or equal to three times the upper limit of normal (ULN) occurred in 0.7% of the 935 lacosamide recipients and 0% of the 356 placebo recipients. Hepatitis (transaminases greater than twenty times the ULN) and nephritis (proteinuria and urine casts) was reported in a healthy subject 10 days after lacosamide administration was completed. Without any specific intervention, transaminase levels returned to normal within one month. Serological tests indicated a negative result for viral hepatitis and bilirubin levels were normal. The hepatitis/nephritis was considered to be a delayed hypersensitivity reaction to lacosamide.
- The tolerability profile of short-term intravenous lacosamide was similar, apart from local reactions, to that of oral lacosamide in patients with partial-onset seizures, according to data from a 2-day, randomized, double-blind, double-dummy, placebo-controlled study[23] Sixty inpatients (aged 19–61years), previously treated with oral lacosamide, were randomized to either oral lacosamide (plus placebo infusion) or 30- or 60-minute intravenous lacosamide infusions (plus oral placebo).[23] The intravenous lacosamide dosage (200–600 mg/day) was the same as the dosage of oral lacosamide that patients had previously received during an open-label extension study.
- Treatment-emergent events associated with intravenous lacosamide were mild or moderate in intensity and included dizziness, headache, back pain and somnolence.[23] Infusion site-related adverse events were infrequent and did not result in discontinuations.[23]
- When used as short-term replacement for oral lacosamide, intravenous lacosamide was well tolerated when administered as a 10-, 15- or 30-minute infusion, according to data from an open-label study in which 160 patients received intravenous lacosamide for 2–5 days.[36] Patients had previously been treated with oral lacosamide 200–800 mg/day. The incidence of adverse events was similar when lacosamide as administered as a 10-, 15- or 30-minute infusion, with headache (5%, 7%, 8%) and dizziness (5%, 6%, 8%) being most commonly reported.

5. Dosage and Administration

Lacosamide is indicated in the US[9] and EU[6] for use as adjunctive therapy in the treatment of partial onset seizures in adult patients with epilepsy. Lacosamide is available as a tablet (EU and US) or syrup (EU only) for oral use or as an injection for intravenous use (EU and US). Lacosamide for infusion is an alternative for patients when oral administration is temporarily not feasible. Lacosamide should be taken twice daily, with an initial starting dose of 50 mg twice daily (100 mg/day). Lacosamide can be increased at weekly intervals by 100 mg/day (administered as two divided doses) up to the recommended maintenance dosage of 200 or 400 mg/day, depending on response and tolerability. Lacosamide can be taken with or without food. The discontinuation of lacosamide should be gradual (such as tapering the daily dose by 200 mg each week).

If administered intravenously, the lacosamide solution should be infused, with or without dilution,[6] over a period of 30–60 (US)[9] or 15–60 minutes (EU).[6] The conversion of lacosamide from oral to intravenous administration or *vice versa* can be achieved directly without titration, with the twice-daily and total daily dosage being maintained.

In the EU and US,[6,9] caution is advised when lacosamide is administered to patients with severe cardiac disease (e.g. myocardial ischaemia or heart failure) and those taking drugs known to induce PR

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interval prolongation. In the US,[9] caution is advised when lacosamide is administered to patients with known heart conduction problems (e.g. marked first-degree AV block, second-degree or higher AV block and sick sinus syndrome without pacemaker). In the EU,[6] lacosamide is contraindicated in patients with known second- or third-degree AV block.[6]

Local prescribing information should be consulted for detailed information, including warnings, contraindications, precautions, drug interactions and use in special patient populations.

6. Lacosamide: Current Status in Partial-Onset Seizures

Lacosamide is approved in the EU[6] and US[9] for use as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients with epilepsy aged ≥16[6] or ≥17[9] years. In three randomized, placebo-controlled, multicentre studies, with a 12-week maintenance phase, oral lacosamide 200 and 400 mg/day was effective in patients with partial-onset seizures despite prior treatment with at least two AEDs. Oral lacosamide was generally well tolerated. In patients who are temporarily unable to take oral lacosamide, short-term (≤5 days) treatment with intravenous lacosamide represents a well tolerated alternative. Three ongoing open-label extension studies are investigating the long-term efficacy of adjunctive lacosamide in patients with partial seizures.[18,31-33] Interim analysis of one of these studies demonstrated the long-term efficacy and tolerability of oral lacosamide in this patient population.

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