Lacosamide (LCM) is a recently approved anticonvulsant in Europe and the USA. Efficacy data showed fast onset of anticonvulsant effects and significant reduction of partial-onset seizures, even in a severely refractory population. LCM is well tolerated, with the most common adverse event being dizziness, followed by headache, nausea and diplopia. LCM also provides a novel mechanism of action and favorable pharmacokinetic profile that includes absolute bioavailability, low protein binding, renal excretion, lack of hepatic enzyme induction or inhibition, low potential for drug–drug interactions, and a relatively long half-life. LCM can also be given as intravenous solution without significant cardiac side effects. Considering the fact that more than 30% of epilepsy patients remain refractory despite various anti-epileptic drugs, LCM may provide added benefit to patients with refractory seizures.

Keywords: lacosamide • new anticonvulsant • partial seizure • slow inactivation • sodium channel • status epilepticus • Vimpat®

Epilepsy is one of the most common and serious neurological disorders, affecting people of all ages [1]. A total of 10% of the world’s population have at least one epileptic seizure in a lifetime, and a third of these develop recurrent seizures with diagnosis of epilepsy. It is estimated that epilepsy affects 1–2% of the world’s population. Despite the advent of new anti-epileptic drugs (AEDs) over the past few decades, approximately 30–40% of people with epilepsy will fail to become seizure free [2,3] and many experience undesirable side effects. Future advances in treatment and prevention of epilepsy will depend on the development of new medical and surgical treatment, which could reduce seizure frequency and severity as well as improve tolerability and safety.

Lacosamide (Vimpat®; LCM), (R)-2-acetamido-N-benzyl-3-methoxypropionamide, is a functionalized amino acid molecule with a chemical structure based on the d-serine moiety [4–6]. It was previously known as harkoseride or SPM 927. Based on the efficacy and therapeutic index observed in a range of animal models of epilepsy, LCM was subsequently developed as an AED for both oral and intravenous use. LCM was approved as an adjunctive treatment for partial-onset seizures in patients of at least 16 years by the European Medicines Agency (August 2008) [101] and in patients 17 years or older by the US FDA (October 2008) [102]. LCM is also available in oral syrup in Europe (15 mg/ml) and oral solution in the USA (10 mg/ml). Clinically relevant main properties of LCM are summarized in Table 1.

Pharmacokinetics

Lacosamide has a linear pharmacokinetic profile with high oral bioavailability [7]. Studies in healthy volunteers demonstrated that LCM is rapidly and completely absorbed [8–10]. The rate and extent of absorption are not affected by the presence of food [8]. Peak
serum concentrations occur at 1–4 h after oral intake, and the elimination half-life of LCM is approximately 13 h, allowing convenient twice-daily dosing [5,7,11]. LCM is primarily eliminated renally as unchanged drug (>40%) and an inactive metabolite, O-desmethyl metabolite (<30%) via CYP2C19 [5,7,8,11]. For patients with severe renal impairment (creatinine clearance of ≤30 ml/min) and in patients with end-stage renal disease, a maximal recommended dose of LCM is 300 mg/day in the USA, and 250 mg/day in Europe [101,102]. In subjects with moderate hepatic impairment, LCM should be titrated with caution and the recommended maximal dose is 300 mg/day in the USA [101], whilst no specific dose adjustment is recommended in Europe.

Lacosamide is highly water soluble and can be given intravenously. The recommended intravenous infusion rate of LCM is over 30 min and the C<sub>max</sub> is reached at the end of infusion. Studies in healthy volunteers demonstrate bioequivalence for C<sub>max</sub> and AUC for both the 30- and 60-min infusion durations [12]. Infusion over 15 min was near bioequivalent, with a slightly higher C<sub>max</sub> but equivalence for AUC [12]. The volume of distribution is approximately 0.6 l/kg, which is similar to body water volume [10]. The pharmacokinetics of both oral and intravenous LCM are dose-proportional (up to 800 mg), with low intra- and inter-subject variability.

Plasma protein binding is less than 15%, which minimizes the potential for displacement of other drugs [13] and drug–drug interactions. At present, there is no indication that LCM acts as an inducer or inhibitor of the cytochrome P450 (CYP450) isoenzymes, except for the inhibition of CYP2C19 in vitro at concentrations more than 15-fold higher than therapeutic plasma levels [9]. Specific drug-interaction studies involving carbamazepine, valproic acid, omeprazole, metformin, digoxin and an oral contraceptive (ethinylestradiol and levonorgestrel) demonstrated no clinically relevant influence on the pharmacokinetics of these drugs [13,14]. However, the plasma concentration of LCM can be lowered by 15–20% when coadministered with carbamazepine, phenytoin or phenobarbital [101].

### Mechanisms of action

The precise mechanisms by which LCM exerts its antiepileptic effect in humans are not fully understood, but a novel mode of action has been suggested. LCM selectively enhances slow inactivation of voltage-gated sodium channels (VGSCs), which may normalize neuronal firing thresholds [15]. Unlike other classical AEDs, such as carbamazepine, phenytoin and lamotrigine, which act on fast inactivation of VGSCs, LCM selectively enhances the slow inactivated state of VGSCs, which promotes the inhibition of sustained repetitive firing of neurons [15]. When depolarized from their resting state, VGSCs open to allow intracellular influx of sodium, which then generates action potentials. Following depolarization, VGSCs changes into a ‘fast inactivated state’ over a few milliseconds before reverting back to the resting state. However, when neurons are firing rapidly and repetitively, VGSCs may change into a ‘slow inactivated state’ through structural or conformational rearrangement of the sodium channel pore that develops over several seconds.

Preclinical studies demonstrated potent anticonvulsant activity of LCM in a broad range of animal models of partial onset and pharmacoresistant seizures, generalized tonic–clonic seizures, as well as status epilepticus.

### Table 1. Main properties of lacosamide.

<table>
<thead>
<tr>
<th>Property</th>
<th>Details</th>
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</thead>
<tbody>
<tr>
<td>Indications</td>
<td>Adjunctive therapy for partial seizures in adults</td>
</tr>
<tr>
<td>Approval status</td>
<td>Approved by both EMA and FDA</td>
</tr>
<tr>
<td>Mode of action</td>
<td>Selective enhancement of slow inactivation of voltage-gated sodium channels</td>
</tr>
<tr>
<td>Starting dose</td>
<td>100 mg/day</td>
</tr>
<tr>
<td>Therapeutic dose</td>
<td>200–400 mg/day</td>
</tr>
<tr>
<td>Dosing schedule</td>
<td>Twice-daily</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Alimentary, oral (tablet and syrup/solution), parenteral, intravenous</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>13</td>
</tr>
<tr>
<td>Time to C&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>1–4</td>
</tr>
<tr>
<td>Oral bioavailability (%)</td>
<td>~100</td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>&lt;15</td>
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<tr>
<td>Chemical structure</td>
<td><img src="https://example.com/chemical_structure.png" alt="Chemical structure" /></td>
</tr>
</tbody>
</table>
Intraperitoneal LCM is effective in preventing seizures in the 6-Hz psychomotor seizure model (ED$_{50}$ 9.99 mg/kg) and audiogenic seizure model (ED$_{50}$ 0.63 mg/kg). LCM 20 and 50 mg/kg completely prevented tonic convulsions induced by maximal electroconvulsive shock and 50 mg/kg provided partial protection against clonic convulsions induced by NMDA in mice [6,16]. LCM was also effective in amygdala and hippocampal kindling models [16,17] as well as a homocysteine-cobalt-induced status epilepticus model, stopping limbic seizures induced by self-sustaining status epilepticus in rats within 15 min of administration of LCM and preventing their recurrence over 24 h [6]. However, LCM was inactive against clonic seizures induced by pentylenetetrazole (EC$_{50}$ ~25 mg/kg), bicuculline (EC$_{50}$ >50 mg/kg) or picrotoxin (EC$_{50}$ >30 mg/kg) in rodents [6,16].

Clinical studies

Three pivotal studies (one Phase II and two Phase III studies) have been conducted to establish the efficacy and safety of LCM [18-20]. The primary assessment of efficacy was measured by the change in seizure frequency per 28 days from baseline to the maintenance period, and the proportion of patients who experienced a 50% or greater reduction in seizure frequency from baseline to maintenance period (50% responder rate). The primary efficacy analysis was conducted on the intent-to-treat (ITT) population, which is defined as all randomized patients who received at least one dose of the trial medication and had at least one post-baseline efficacy assessment.

In the Phase II study [18], three doses of LCM (200, 400 and 600 mg/day) were administered as adjunctive therapy for patients with partial epilepsy with or without secondary generalization (n = 418), with a starting dosage of 50 mg twice-daily, followed by a weekly increase of 100 mg/day to the target dose. Titration phase was followed by a 12-week maintenance phase with an option for continued open-label treatment. Most patients in the study (84%) were taking two antiepileptic agents when LCM therapy was added, and the median seizure frequency was 11–13 per 28 days at baseline. In the ITT population, the median percent reduction in seizure frequency per 28 days from baseline to maintenance was 10% for placebo, 26% for LCM 200 mg/day (p = 0.101), 39% for LCM 400 mg/day (p = 0.002) and 40% for LCM 600 mg/day (p = 0.008). The 50% responder rates were 32.7% for 200 mg/day (p = 0.090), 41.1% for 400 mg/day (p = 0.004) and 38.1% for 600 mg/day (p = 0.014), compared with 21.9% for the placebo group [18].

There were two Phase III trials. One was conducted in the USA and evaluated LCM dosages of 400 and 600 mg/day (n = 405) [19], and the other was mainly conducted in Europe and Australia, evaluating LCM 200 and 400 mg/day compared with placebo (n = 485) [20]. The study design was similar to the Phase II study: LCM was initiated at 100 mg/day and titrated in 100-mg increments per week until the target dose was met. In the US study, significant seizure improvement was observed in both the LCM 400 and 600 mg/day groups. In the ITT population, the median percent reduction in seizure frequency per 28 days from baseline to maintenance was 20.8% for placebo, 37.3% for LCM 400 mg/day (p = 0.008) and 37.8% for LCM 600 mg/day (p = 0.006). The 50% responder rates were 38.3% for 400 mg/day (p < 0.001) and 41.2% for 600 mg/day (p < 0.001), compared with 18.3% for placebo. Of 317 patients completing maintenance, nine were seizure free throughout the 12-week maintenance period (placebo: 0%; 400 mg/day: 2.5%; 600 mg/day: 8.1%) [19]. In the analysis by seizure type, the largest reductions were observed for secondarily generalized tonic–clonic seizures, and these reductions appeared to be dose-related. The observed median percent reduction for secondarily generalized tonic–clonic seizures was 93.0% for the LCM 600 mg/day group and 59.4% for the LCM 400 mg/day group compared with 14.3% for placebo. The corresponding responder rates were 70.2% for the 600 mg/day group and 56.0% for the 400 mg/day group, compared with 33.3% for placebo. Evidence for a dose-related reduction in seizure frequency was also observed for complex partial seizures, but not for simple partial seizures [19]. For the study in Europe and Australia, median percent reduction in seizure frequency in the ITT population was 20.5% for placebo, 35.3% for LCM 200 mg/day (p = 0.02) and 36.4% for 400 mg/day (p = 0.03). The 50% responder rate for LCM 400 mg/day (40.5%) was significant (p = 0.01) over placebo (25.8%), but was not for 200 mg/day (35.0%) [20].

Subsequent analysis of pooled efficacy data from these trials further supports the overall efficacy of LCM at doses of 200–600 mg/day [21,22]. For the pooled analysis, the 50% responder rates per 28 days from baseline to the maintenance period were 22.6% for placebo, 34.1% for LCM 200 mg/day, and 39.7% for LCM 400 mg/day. The median percent reduction in seizure frequency was 18.4% for placebo, 33.3% for LCM 200 mg/day and 36.8% for LCM 400 mg/day [21,22]. Overall, the LCM 600 mg/day group showed similar efficacy to the 400 mg/day group. For those who completed the maintenance period, pooled analysis demonstrates that complete seizure freedom during the maintenance period was achieved in 2.7, 3.3 and 4.8% of patients randomized to LCM 200, 400 and 600 mg/day, respectively, compared with 0.9% in the placebo group [21,22]. LCM onset of action appears rapid, since there was already
a significant seizure reduction compared with placebo as early as the first week when patients were receiving 100 mg/day regardless of assigned dose group in the pooled analysis (median percent reduction in seizure frequency: 33.0 vs 19.4%; p < 0.01) [23].

Safety & tolerability
Among patients randomized to LCM, dizziness, headache, nausea, diplopia, blurry vision and tremor were the most common treatment-emergent adverse events (TEAEs) with an incidence of at least 10% during the treatment period (both in titration and maintenance phases). All of these TEAEs were dose-related and discontinuation due to TEAEs were 8% in the LCM 200 mg/day, 17% in the 400 mg/day and 29% in the 600 mg/day groups, compared with 5% of placebo recipients [101,102]. The incidence of cognitive side effects (i.e., memory impairment, confusion or disturbance in attention) were very similar to placebo during the treatment period (7% for placebo vs 9% for LCM), suggesting that LCM could be well tolerated in terms of cognitive side effects. Clinical laboratory serum tests and vital sign measurements across treatment groups did not identify any changes that appeared to be associated with LCM. Electrocardiographic studies showed no significant changes in heart rate, QTc interval or QRS duration after LCM exposures. However, a small increase in mean PR interval in electrocardiogram at the end of maintenance (1.4–6.6 ms increase) was noted. There were no reports of adverse events associated with PR interval prolongation, and the degree of increase is considered to be similar to other AEDs, such as carbamazepine (8–16 ms increase), lamotrigine (5 ms increase) and prebagalin (<5 ms increase) [24–27]. The incidence of rash was low for patients randomized to LCM, similar to that reported with placebo (3%). No rashes were serious and all were assessed as mild-to-moderate in intensity. LCM showed minimal effect on body weight and the mean weight changes after 18 weeks of LCM exposure were +0.6 kg for placebo, +0.1 kg for 400 mg/day and +0.2 kg for 600 mg/day [19].

The tolerability profile of the intravenous infusion of LCM was similar to oral LCM. TEAEs associated with intravenous LCM were mild or moderate in intensity and included dizziness, headache, back pain and somnolence. Infusion site-related pain was infrequent (0% in 60 min infusion and 11% in 30 min infusion), and did not result in discontinuations of LCM [28]. Another open-label study (n = 160) demonstrated that faster infusion of LCM is also well tolerated; LCM was infused over 10, 15 or 30 min for 2–5 days (200–800 mg/day), and the incidence of TEAEs was similar to slow infusion with headache (5, 7 and 8%) and dizziness (5, 6 and 8%) being most commonly reported [12].

In a human abuse potential study, single-dose administration of LCM 800 mg produced subjective euphoria-type responses in 15% of subjects (5/34), compared with 0% in the placebo group even though the rate of euphoria at therapeutic doses in other clinical studies was less than 1% [101,102]. The reported euphoria-type responses were similar to those produced by alprazolam, but the duration of the euphoria was shorter. Two other pharmacokinetic studies also showed euphoria-type responses following single and multiple doses of LCM 300 mg and 800 mg (ranging from 6–25%) compared with placebo (0%) [101,102]. Due to this possible abuse potential, LCM is designated as schedule V.

Future perspective
Previous clinical studies demonstrated that LCM is well tolerated and effective in controlling partial-onset seizures as adjunctive therapy. Although the efficacy data from the clinical trials were not noticeably different from that of already existing AEDs, the main advantages of LCM are its favorable pharmacokinetic profile, availability of an intravenous solution and a different mechanism of action. Since many patients tend to take concurrent AEDs and other medications, LCM’s low potential for drug–drug interaction along with no relevant effect on CYP450, complete absorption and low protein binding may boost its clinical use in epilepsy patients in the future. Intravenous LCM solution is packaged as 200 mg/20 ml per vial and can be mixed with various diluents, such as sodium chloride injection, dextrose injection and lactated Ringer’s injection, even though LCM injection does not require dilution. Since LCM’s enhancement of the slow inactivated state of VGSCs promotes the inhibition of sustained repetitive firing of neurons, it has been speculated that LCM could be a useful addition in the treatment of status epilepticus. In fact, there are recent case reports illustrating successful treatment of status epilepticus with LCM [29–31]. Many drugs that are used to control status epilepticus are commonly associated with sedation, respiratory suppression, hypotension, cardiac dysrhythmia, hepatic toxicity and anaphylactic reactions when they are given intravenously at high loading dosages. Therefore, LCM may be an attractive alternative treatment for status epilepticus because these adverse effects are less common with LCM, although the efficacy and safety of intravenous LCM has not yet been established in the treatment of status epilepticus. Additional prospective studies are needed and, until then, the use of intravenous LCM in status epilepticus should be reserved for carefully selected patients. As discussed earlier, cognitive side effects were not one of the common side effects of LCM, which could be a significant
Lacosamide as a new add-on therapy for the treatment of partial-onset seizures

Review: Clinical Trial Outcomes

Lacosamide (LCM) is a new anticonvulsant with a proposed novel mechanism of action and favorable pharmacokinetic profile. Clinical studies have shown fast onset of anticonvulsant effects and a significant reduction of partial-onset seizures at a dose of 200–600 mg/day. LCM was well tolerated with the most common adverse event being dizziness, followed by headache, nausea and diplopia. LCM was substantially less associated with sedation, cognitive dysfunction, rash and mood disorders when compared with many other existing anti-epileptic drugs.

Although some preclinical studies and case reports suggest that LCM could be potentially effective against generalized onset seizures [35], there has been no prospective human study to establish LCM as a broad-spectrum AED. Recently, multicenter clinical studies have just begun to evaluate the safety of LCM as an adjunctive therapy in patients with primary generalized epilepsy. Clinical studies in the pediatric population (aged <16 years) are also needed, and a clinical study is ongoing for partial epilepsy in children.

Financial & competing interests disclosure
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Executive summary
- Lacosamide (LCM) is a new anticonvulsant with a proposed novel mechanism of action and favorable pharmacokinetic profile.
- Clinical studies have shown fast onset of anticonvulsant effects and a significant reduction of partial-onset seizures at at dose of 200–600 mg/day.
- LCM was well tolerated with the most common adverse event being dizziness, followed by headache, nausea and diplopia.
- LCM was substantially less associated with sedation, cognitive dysfunction, rash and mood disorders when compared with many other existing anti-epileptic drugs.

Bibliography
23 Sperling M, Rudd D, Hebert D, Doty P. Early onset of efficacy in the initial weeks of treatment with lacosamide: a pooled analysis of three Phase II/III trials. Epilepsia 49(Suppl. 7), 457 (2008).
32 Degojorto CM. Atrial flutter/atrial fibrillation associated with lacosamide for partial seizures. Epilepsy Behav. 18, 322–324 (2010).

■ Websites