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Expert Opinion on Pharmacotherapy

Aims and scope

Expert Opinion on Pharmacotherapy is a MEDLINE-indexed, peer-reviewed, international journal publishing review articles and original papers on newly approved/near to launch compounds, providing expert opinion on the likely impact of these new agents on existing pharmacotherapy of specific diseases.

The Editors welcome:

- *Reviews* covering new drugs/drug classes for specific diseases, from development Phase III to those that have been available to pharmacopoeia for up to 5 years, and their potential impact on future treatment strategies
- *Drug Evaluations* reviewing the clinical and pharmacological data on a particular drug
- *Original Research* papers reporting the results of clinical investigations on agents that are in Phase III and IV clinical trials and pharmacologically based studies with a strong link to clinical practice

The audience consists of research and development, regulatory and marketing decision makers in the pharmaceutical industry and decision makers in healthcare provision.

Editorial policy

Articles published in *Expert Opinion on Pharmacotherapy* are commissioned by the Commissioning Editor in collaboration with the Editorial Board. Authors who wish to contribute should contact the Commissioning Editor. All reviews and drug evaluations are subject to anonymous peer-review.

Editorial boards

The Editorial Board is composed of senior scientists involved in drug research and development. The Board are responsible for selecting authors and topics for review to ensure comprehensive coverage of subjects in each therapeutic area.

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Expert Opinion

Lacosamide: new adjunctive treatment option for partial-onset seizures

Steve S Chung
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Importance of the field: Epilepsy is one of the most common neurological disorders, affecting up to 2% of the population worldwide. Studies show that patients with refractory seizures have higher morbidity and mortality rates, as well as a poorer quality of life, than those with controlled seizures. Therefore, treatment that reduces the frequency of seizures may improve patients' quality of life. Lacosamide (LCM) is a recently approved anticonvulsant in Europe and the USA which offers new mechanisms of action and favorable safety profiles. Efficacy data have shown fast onset of anticonvulsant effects and significant reduction of partial-onset seizures as adjunctive therapy at LCM 200 and 400 mg/day, even in a severely refractory population.
Areas covered in this review: This article reviews three pivotal clinical trials of LCM, including its efficacy and tolerability over 7 years. In addition, LCM's key pharmacodynamics and pharmacokinetics from a search of the literature are reviewed in detail. This article also includes recent publications on the safety and use of intravenous LCM solution for patients with epilepsy.
What the reader will gain: This article provides comprehensive review of efficacy and safety information of LCM along with comprehensive pharmacokinetic information, which includes absolute bioavailability, low protein binding, lack of hepatic enzyme induction or inhibition, and low potential for drug-drug interactions.
Take home message: Considering the fact that more than 30% of epilepsy patients remain refractory despite various antiepileptic drugs, LCM may provide added benefit to patients with refractory seizures.

Keywords: lacosamide, new anticonvulsant, partial seizures, slow inactivation, sodium channels, Vimpat

Expert Opin. Pharmacother. (2010) 11(9):1595-1602

1. Introduction

Epilepsy is one of the most common neurological disorders affecting up to 2% of the population worldwide, and almost 2 million people in the USA alone [1]. Treatment of epilepsy often imposes an exposure to various antiepileptic drugs (AEDs) and requires long-term commitment and compliance from the patient [2]. Excluding the small percentage of people who have undergone successful epilepsy surgery, the vast majority of patients are maintained through chronic medical management for appropriate seizure control. Despite the advent of new AEDs over the past 15 years, ~ 30% of epilepsy patients still experience recurrent seizures and many experience undesirable side effects [3,4]. Therefore, there are still unmet needs for the treatment of epilepsy and there remains a need to develop new AEDs that could reduce seizure frequency and severity as well as improve tolerability and safety.

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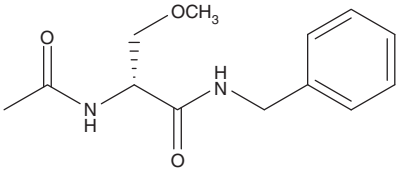
Box 1. Drug summary.

Drug name	Lacosamide
Phase	Launched
Indications	Epilepsy, partial (focal, local)
Pharmacology description	Voltage-gated sodium channel inhibitor Collapsin-response mediator protein 2 binding
Route of administration	Alimentary, p.o. Parenteral, intravenous
Chemical structure	
Pivotal trial(s)	Phase II: SP667 (Ben-Manachem) Phase III: SP754 (Chung) Phase III: SP755 (Halasz)

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2. Lacosamide

Lacosamide (LCM; **Box 1**), (R)-2-acetamido-*N*-benzyl-3-methoxypropionamide, previously known as harkoseride or SPM 927, is a functionalized amino acid with a novel anticonvulsant activity [5-7]. Its chemical structure is shown in **Box 1**. Based on the efficacy and therapeutic index observed in a range of animal models of epilepsy at the National Institutes of Health (NIH) Anticonvulsant Screening Program, LCM was subsequently developed as an AED for both oral and intravenous use. LCM has been approved as an adjunctive treatment for partial-onset seizures in patients aged ≥ 16 years by the European Commission (August 2008) and in patients aged ≥ 17 years by the FDA (October 2008).

3. Pharmacodynamics

LCM has demonstrated potent anticonvulsant activity in a broad range of animal models of partial onset and pharmaco-resistant seizures, generalized tonic-clonic seizures, as well as status epilepticus. Intraperitoneal LCM was effective in preventing seizures in the 6-Hz psychomotor seizure model (ED_{50} 9.99 mg/kg) and the audiogenic seizure model (ED_{50} 0.63 mg/kg). LCM 20 and 50 mg/kg completely prevented tonic convulsions induced by maximal electroconvulsive shock (MES), and 50 mg/kg provided partial protection against clonic convulsions induced by NMDA in mice [7,8]. LCM has also been effective in amygdala and hippocampal kindling models [8,9]. In hippocampal kindling rats, the activity of LCM (25 mg/kg) was superior to that of maximally effective doses of phenytoin (150 mg/kg), carbamazepine (50 mg/kg), valproic acid (250 mg/kg) and ethosuximaide (250 mg/kg) [7]. 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 [7,8]. LCM was effective in a homocystein-cobalt-induced status epilepticus model, stopping limbic seizures induced by self-sustaining status epilepticus in rats within 15 min of administration and preventing their recurrence over the following 24 h [7].

The precise mechanisms by which LCM exerts its antiepileptic effect in humans are not fully understood, but a new mode of action has been suggested. LCM selectively enhances slow inactivation of voltage-dependent sodium channels (VGSCs) without affecting fast inactivation, which may normalize neuronal firing thresholds (**Table 1**) [10]. VGSCs control sodium ion influx across the cell membranes and can adopt different conformational states in response to changes in membrane potential. When depolarized from their resting state, VGSCs open to allow the influx of sodium ions into the cell, which then generate the action potential. Following depolarization, VGSCs change to a 'fast inactivated state' over milliseconds before reverting back to the resting state. However, when neurons are firing rapidly and repetitively, VGSCs may undergo a 'slow inactivated state' through structural or conformational rearrangement of the sodium channel pore, which develops over several seconds. 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 [10]. In preclinical experiments, lacosamide has also been shown to bind to collapsin response mediator protein 2 (CRMP-2), which is involved in neuronal differentiation, regulation of gene expression, polarization and axonal outgrowth [7]. The role of CRMP-2 binding in seizure control is unknown at this time, but it may be a factor in the disease-modifying potential of LCM.

4. Pharmacokinetics and metabolism

LCM has a linear pharmacokinetic profile with high oral bioavailability [11]. Studies in healthy volunteers have demonstrated that LCM is rapidly and completely absorbed [12-14]. The rate and extent of absorption are not affected by the presence of food [12]. Following oral intake of LCM, peak serum concentrations occur within 1 – 4 h, and the elimination half-life is ~ 13 h [6,12,15]. LCM has low plasma protein binding (≤ 15%) and the volume of distribution is ~ 0.6 liters/kg, which is similar to body water [14]. The pharmacokinetics of both oral and intravenous LCM are dose-proportional (up to 800 mg), with low intra- and inter-subject variability. Following twice-daily administration of oral LCM, steady-state plasma concentrations are reached after 3 days. The low protein binding of LCM minimizes the potential for displacement of other drugs [16] and, thus, low potential for drug–drug interactions. In addition, LCM has minimal

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