CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	22-253, 22-254, 22-255
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	9/28/07
PRODUCT:	Lacosamide (SPM927) Tablet, Injection, Oral Syrup
INTENDED CLINICAL POPULATION:	epilepsy
SPONSOR:	Schwarz Biosciences
REVIEW DIVISION:	Division of Neurology Products (HFD-120)
PHARM/TOX REVIEWER:	Ed Fisher
PHARM/TOX SUPERVISOR:	Lois Freed
DIVISION DIRECTOR:	Russell Katz
PROJECT MANAGER:	Jackie Ware

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I. INTRODUCTION AND DRUG HISTORY

NDA number: 22-253 (oral tablet), 22-254 (injection), 22-255 (oral syrup)

Date of submission: 9/28/07

Sponsor: Schwarz Biosciences

Drug:

Trade name:

Generic name: lacosamide

Code names: ADD 234037; harkoseride; SPM 927

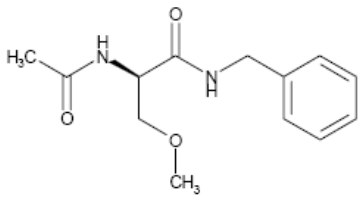
Chemical name: (R)-2-acetamido-N-benzyl-3-methoxypropionamide

CAS registry number: 175481-36-4

Molecular formula: $C_{13}H_{18}N_2O_3$

Molecular weight: 250.3

Structure:



Relevant IND: 57,939

Drug class: sodium channel modulator

Indication: epilepsy

Route of administration: oral (tablets, solution), injection

Previous reviews: Original IND review dated 3/22/99
CAC-EC reviews dated 7/13/00, 3/1/01, and 6/5/02
CAC-EC minutes dated 8/8/00, 4/24/01, and 7/9/02

Tables and figures are taken directly from the sponsor's submission unless noted otherwise.

II. PHARMACOLOGY

A. BRIEF SUMMARY

Lacosamide (LCM) is a member of a series of functionalized amino acids that were specifically synthesized as anticonvulsant drug candidates. In standard in vitro radioligand binding assays, LCM showed no significant affinity for any of the typical binding sites, including a variety of neurotransmitter, neuropeptide, and growth factor receptors, ion channels, transporters, and intracellular signaling enzymes. However, weak displacement of binding (25% at 10 uM) was observed for the sodium channel site 2. Electrophysiological studies indicated that LCM selectively enhances the slow inactivation of sodium channels without affecting fast inactivation. This was shown to be in contrast to other sodium channel modulators such as lamotrigine, phenytoin, and carbamazepine which enhance fast inactivation. No significant modulation of voltage-gated potassium (KCNQ2/3) or calcium channels (L-, N-, P- and T-type) was detected.

In studies using proteomic affinity-labeling techniques, collapsin-response mediator protein 2 (CRMP-2; also called DRP-2, dihydropyrimidinase-related protein) was subsequently identified as a potential binding target of LCM. In radioligand binding experiments using a cloned human analogue of CRMP-2 expressed in Xenopus oocytes, LCM exhibited a binding affinity of 5 μM.

Due its structural relationship to the endogenous amino acid D-serine, which acts as an NMDA receptor antagonist, LCM was assessed for binding at glutamate receptors. In an initial experiment, 50% displacement of a glycine site antagonist was observed with an IC50 of 5.2 µmol/L. However, in a follow-up study using more specific ligands, LCM (10 µmol/L) did not produce significant (>50%) displacement of specific binding at AMPA, kainate, NMDA (agonist, glycine and phencyclidine binding sites) or glycine receptors isolated from rat brain. But in a functional experiment using recombinant NMDA receptor subtypes, LCM inhibited NMDA- and glycine-induced currents at NR1/2B receptors, albeit with an IC50 of 1.89 mmol/L.

LCM showed anticonvulsant activity in various rodent seizure models, ie, maximal electroshock seizures (MES), 6 Hz seizures, hippocampal kindling, audiogenic seizures (AGS), and self sustaining status epilepticus (SSSE). Lacosamide was inactive against clonic convulsions induced by sc pentylenetetrazol (PTZ), bicuculline, and picrotoxin, but it did inhibit NMDA-induced convulsions in mice. Although inactive against sc PTZ-induced threshold clonic convulsions, LCM elevated the seizure threshold somewhat in the iv PTZ test at the MES ED50. The O-desmethyl metabolite, SPM 12809, and the S-entantiomer of LCM, SPM 6953, were inactive in the MES test at relevant doses.

In vitro investigations of the cardiovascular effects of LCM showed that LCM reduced the action potential duration in cardiac tissue and inhibited sodium current in isolated cells. Effects on sodium current were dependent on membrane potential, with higher inhibition at more depolarized potentials. In vivo studies showed that LCM decreased cardiac conduction. In anesthetized instrumented dogs, LCM induced hypotensive effects characterized mainly by reduced contractility, as indicated by decreases in systolic left ventricular pressure and left ventricular pressure over time (dP/dt) and reduced cardiac output. These effects were accompanied by increases in PR interval and QRS complex duration and by AV block. Similar EEG effects were seen in monkeys, ie, QRS prolongation and AV and ventricular block.

B. MECHANISM OF ACTION

LCM (10–100 μM) showed no significant affinity (>50% inhibition) for any of the typical receptors, channels, or enzymes screened, but did bind weakly (25–50% inhibition) to the sodium channel at the batrachotoxin site 2. LCM did not modulate the uptake of NE, DA, or 5HT into synaptosomes, and did not bind to GABA transporters or influence the activity of GABA transaminases. The

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