CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-253 & 22-254

PHARMACOLOGY REVIEW(S)

Tertiary Pharmacology Review

By: Paul C. Brown, Ph.D., ODE Associate Director for Pharmacology and Toxicology OND IO
NDA: 22-253, 22-254, —— b(4)
Submission date: September 28, 2007
Drug: lacosamide (tablet)
Sponsor: Schwarz Biosciences
Indication: treatment of Epilepsy as adjunctive therapy in patients with partial onset seizures aged 16 years and older

Reviewing Division: Division of Neurology Products

Introductory Comments: Thes—— NDAs have been submitted for the same drug substance and essentially same indication. The —— NDAs differ in the formulation of the drug product. NDA 22-253 is for a tablet, 22-254 is for an injectable formulation ——). Another NDA —— was submitted to the Division of Anesthesia, Analgesia and Rheumatology Products for the management of neuropathic pain associated with diabetic peripheral neuropathy. b(4)

The pharm/tox reviewer and supervisor found the nonclinical information submitted for lacosamide to be sufficient to support its use for the proposed indication.

Reproductive and developmental toxicity:
The sponsor has proposed a pregnancy category of C. The reviewer and supervisor agree with this category.

The reproductive and developmental studies did not indicate that lacosamide was teratogenic but some embryofetal and perinatal mortality and growth deficits were observed. In addition, a juvenile animal study in which rats were treated beginning on postnatal day seven demonstrated some neurobehavioral changes, brain weight decrease and delay in sexual maturation in females. I agree that these studies support a pregnancy category of C. I agree with the supervisory memo that additional embryofetal studies are not needed at this time.

Neurotoxicity:
The reviewer recommended that the sponsor should examine the effects of lacosamide on brain development during the prenatal and early postnatal periods using more sensitive techniques for assessing CNS structure and function than were employed in the standard pre- and postnatal development study.

Because of the apparent neurobehavioral effects observed in the juvenile animal study, and the potential serious consequences of neurotoxicity in children, I agree that further assessment can be requested from the sponsor after approval.

Conclusions:
I concur with the Division pharm/tox conclusion that the nonclinical data support approval of this NDA.

I concur with the recommendation for collecting additional developmental neurotoxicity data post approval.

I agree with the labeling changes suggested in the supervisory memo including deletion of section [redacted] b(4)

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Paul Brown
7/17/2008 03:17:20 PM
PHARMACOLOGIST

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: July 16, 2008

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: Lacosamide (SPM927) Tablet (NDA 22-253), Injection (NDA 22-254), [redacted] submitted September 28, 2007 b(4)

Schwarz Pharma has submitted [redacted] NDAs to the Division of Neurology Products for lacosamide (SPM927):

- NDA 22-253: Lacosamide tablet for "treatment of Epilepsy as adjunctive therapy in patients with partial onset seizures aged 16 years and older".
  - Lacosamide tablet for the "management of neuropathic pain associated with diabetic peripheral neuropathy" is being reviewed by the Division of Anesthesia, Analgesia and Rheumatology Products under NDA
- NDA 22-254: Lacosamide injection for "treatment of Epilepsy as adjunctive therapy in patients with partial onset seizures aged 16 years and older when oral administration is temporarily not feasible".

[redacted] b(4)

The nonclinical data in support of these NDAs were submitted under NDA 22-253 and were cross-referenced in NDAs 22-254 and [redacted] Review of the nonclinical data submitted in support of the oral formulations was shared by DNP and DAARP.

In DNP, J. Edward Fisher, Ph.D. reviewed the following nonclinical studies:

- Pharmacology (i.e., animal efficacy, mechanism of action) relevant to the epilepsy indication.
- Toxicology
  - Sprague-Dawley rat (14-day i.v.)
  - Beagle dog (14-day i.v.)
- Reproductive toxicology
  - Combined oral fertility and developmental toxicity study in Sprague-Dawley rat

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.