CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022255Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	April 20, 2010
To:	Russell Katz, MD, Director Division of Neurology Products (DNP)
Through:	Claudia Karwoski, PharmD, Director Division of Risk Management (DRISK)
From:	Mary Dempsey BS, Risk Management Programs Coordinator, DRISK Jessica Diaz, RN, BS, Patient Labeling Reviewer, DRISK
Subject:	Vimpat Oral Solution proposed REMS ; Vimpat Tablets and Injection proposed REMS Modification
Drug Name(s):	Vimpat (lacosamide)
Application Type/Number:	NDA 022255 Vimpat Oral Solution NDA 022253/S-006 Vimpat Tablets NDA 022254/S-003 Vimpat Injection
Applicant/sponsor:	Schwarz Biosciences, Inc., a member of the UCB Group of Companies
OSE RCM #:	2009-1540

1 Background

The Division of Neurology Products (DNP) requested the Division of Risk Management (DRISK) review the Vimpat (lacosamide) Oral Solution proposed Medication Guide and Risk Evaluation Mitigation Strategy (REMS). DRISK was also requested to review the proposed Medication Guide and proposed Risk Evaluation Mitigation Strategy (REMS) modification for Vimpat (lacosamide) Tablets and Vimpat (lacosamide) Injection.

The proposed REMS (NDA 022255) is for a new commercial Vimpat oral solution and the proposed REMS modification (NDA 022253 and NDA 022254) is for the Vimpat Tablets and Injection. All Vimpat formulations will share the same package insert (PI), Medication Guide (MG) and Risk Evaluation Mitigation Strategy (REMS).

The REMS for Vimpat Tablets and Injection was approved October 28, 2008. The REMS consists of the following elements:

- Medication Guide
- Timetable for Assessment

2 Material Reviewed

- October 28, 2008 Vimpat Tablets and Injection approved REMS
- August 21, 2009 proposed Vimpat Tablets and Injection REMS modification to include a comprehensive Medication Guide
- January 21, 2010 Jessica Diaz' DRISK Review of Patient Labeling (Medication Guide), Proposed Risk Evaluation and Mitigation Strategy, and REMS Supporting Document Amendment
- March 19, 2010 REMS information request to make the elements of the REMS the same for the three Vimpat formulations
- March 31, 2010 proposed comprehensive Medication Guide for the three Vimpat formulations
- April 13, 2010 proposed REMS for Vimpat Oral Solution; proposed REMS modification for Vimpat Tablets and Injection
- April 19, 2010 proposed REMS for the three Vimpat formulations.

3 Proposed REMS Elements

The Vimpat March 31, 2010 submission includes the proposed Medication Guide which incorporated the Vimpat Tablets, Injection, and Oral Solution formulations into one comprehensive Medication Guide.

The Vimpat April 19, 2010 submission includes the proposed REMS which incorporates the Vimpat Tablets, Injection, and Oral Solution formulations into one REMS.

FDA Information Request of March 19, 2010 states the following:

> "The timetable for submission of assessments in the REMS approved on October 28, 2008, for Vimpat (lacosamide) Tablets and Injection requires an April 2010 assessment of the REMS. We acknowledge, however, that subsequent to our initial requirement for a REMS for lacosamide, we determined that all members of the anti-epileptic drug (AED) class, including lacosamide, should have individual Medication Guides that include all risk information that is

> necessary for patients' safe and effective use of each drug, including but not limited to the increased risk of suicidal thoughts and behavior. Thus, the REMS assessment due by April 2010 may consist of a statement that the Medication Guide would be adequate to achieve its purpose."

The title of the April 13, 2010 Vimpat submission is Proposed REMS Modification-Amendment REMS Assessment; however, there is no mention of the REMS Assessment in the submission.

4 Discussion and Conclusion

DRISK performed a comparison of the April 19, 2010 submitted proposed REMS modification and the March 31, 2010 proposed Medication Guide to the approved Vimpat REMS and Medication Guide and found them to be identical with the exception of the inclusion of oral solution text in the REMS and oral solution text and ingredients in the MG; no safety information was added or revised.

5. Recommendation

Approve the Vimpat REMS for all formulations as submitted April 19, 2010.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22255	ORIG-1	SCHWARZ BIOSCIENCES INC	VIMPAT
NDA-22253	SUPPL-6	SCHWARZ BIOSCIENCES INC	VIMPAT
NDA-22254	SUPPL-3	SCHWARZ BIOSCIENCES INC	VIMPAT

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/s/

MARY J DEMPSEY
04/20/2010

MARY E WILLY
04/20/2010
For Claudia Karowski

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation I
Division of Neurology Products

NDA/BLA #s:	22-255
Products:	Vimpat (lacosamide) Oral Solution
APPLICANT:	Schwarz Pharma
FROM:	Russell Katz, M.D., Director
DATE:	01/11/2010

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Vimpat (lacosamide) Oral Solution to ensure that the benefits of the drug outweigh the increased risk of suicidal thoughts and behavior associated with the class of antiepileptic drugs (AEDs), of which Vimpat (lacosamide) Oral Solution is a member. In reaching this determination, we considered the following:

A. It is not possible to precisely estimate the size of the population likely to use Vimpat (lacosamide) oral solution. The estimated number of patients in the United States with partial-onset seizures is approximately 0.9 to 1.8 million. This estimate is based on a US population of about 300 million. The prevalence of epilepsy has been estimated to be 5-10 persons per 1000,[1] with about 60% of these patients having partial seizures.[2]

B. Patients with epilepsy have approximately two to three times the risk of death from any cause compared with persons without epilepsy.[1] Seizures may cause significant trauma, drowning, and accidental injury. Many of the deaths in persons with epilepsy are directly related to seizures, accidents and injuries arising from seizures, and the

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[1] Harrison's Principles of Internal Medicine, 17th Ed. (2008).
[2] Hauser WA, Annegers JF, Rocca WA. Descriptive epidemiology of epilepsy: contributions of population-based studies from Rochester, Minnesota. *Mayo Clin Proc*. 1996;71(6):576–586.

underlying condition resulting in seizures.

C. The efficacy of Vimpat (lacosamide) for the treatment of partial onset seizures was demonstrated in two phase 3 placebo-controlled trials and one supportive phase 2 placebo-controlled trial.

D. If approved, Vimpat (lacosamide) oral solution will be administered on a chronic basis to patients with epilepsy, generally for period of at least 2 years. Such treatment may extend to a lifetime.

E. A known serious risk of AEDs as a therapeutic class is an increased risk of suicidal thoughts and behavior (which are risk factors for completed suicide). The increased risk of suicidal thoughts and behavior were demonstrated in a meta-analysis of randomized, placebo-controlled clinical trial data for 11 AEDs.[3]

   In this meta-analysis, the odds ratio for suicidal behavior or ideation for all AEDs studied was 1.80 (95% CI: 1.24, 2.66); 0.37% of all drug-treated patients and 0.24% of placebo-treated patients had an event of suicidal behavior or ideation. This finding was generally consistent among drugs in the data analyzed. It was shared by drugs with varying mechanisms of action and was observed for all indications studied; this observation suggests that the risk applies to all antiepileptic drugs regardless of indication of use.

   The background incidence of suicide in patients with epilepsy is estimated as being higher than the incidence of suicide in the general population. Estimates of the incidence of suicide in patients with epilepsy vary widely, but studies have consistently indicated a higher incidence of suicide (and suicide attempts) in patients with epilepsy.

   In addition to suicidal ideation, Vimpat (lacosamide) has been associated with various other serious adverse effects that include a hypersensitivity syndrome that may affect multiple organ systems (Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS]), cardiac conduction abnormalities (heart block), syncope, dizziness and ataxia.

F. Vimpat (lacosamide) Oral Solution is not a new molecular entity. It is already approved in tablet form.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Vimpat (lacosamide) Oral Solution. FDA has determined that Vimpat (lacosamide) Oral Solution poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Vimpat (lacosamide) Oral Solution. FDA has determined that Vimpat (lacosamide) Oral Solution is a product for which patient labeling could help prevent serious adverse events. FDA has also determined that Vimpat (lacosamide) Oral Solution has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Vimpat (lacosamide) Oral Solution.

The elements of the REMS will be a Medication Guide and a timetable for submission of assessments of the REMS.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
SAFETY-547	ORIG-1	NO FIRM	antiepileptic drugs
NDA-22255	ORIG-1	SCHWARZ BIOSCIENCES INC	VIMPAT

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/s/

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