CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022255Orig1s000

OTHER REVIEW(S)

MEMORANDUM

TO: NDA 22-255

FROM: Wendy I. Wilson-Lee, Review Chemist

SUBJECT: CMC Review of Revised Carton and Container Labels

DATE: 4/19/2010

CC: Susan Daugherty, HFD 120 RPM; Don Henry, ONDQA PM; Martha Heimann, ONDQA CMC Lead; Ramesh Sood, ONDQA Branch Chief

Revised Carton and Container Labels

Schwarz provided revised carton and container labels based on FDA comments forwarded to the sponsor on 14-APR-2010. Based on further review, and in concert with DMEPA, we requested the sponsor remove the expression of total lacosamide content per total volume as it may confuse the patient. Figures 1 and 2 represent the final draft carton and container labels.

1 Page of Draft Labeling has been Withheld in Full Immediately Following this Page as B4 (CCI/TS)

Overall Recommendation

The revised carton and container labels are adequate, from a CMC perspective.

Wendy I. Wilson-Lee

Wendy I. Wilson-Lee, Ph.D.
Review Chemist
ONDQA DPA-I

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22255	ORIG-1	SCHWARZ BIOSCIENCES INC	VIMPAT

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/s/

WENDY I WILSON
04/19/2010

MARTHA R HEIMANN
04/19/2010
for Ramesh Sood

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 7, 2010
To:	Russell Katz, MD, Director Division of Neurology Products
Thru:	Carlos Mena-Grillasca, RPh, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Judy Park, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Medication Error and Labeling Review
Drug Name(s):	Vimpat (Lacosamide) Oral Solution 10 mg/mL
Application Type/Number:	NDA 022255
Applicant:	UCB, Inc.
OSE RCM #:	2009-2157 and 2009-2158

CONTENTS

1 INTRODUCTION

This review responds to a request from the Division of Neurology Products (DNP) for the Division of Medication Error Prevention and Analysis (DMEPA) to evaluate the new proposed concentration for the Vimpat oral solution (10 mg/mL) and revised container labels, carton and insert labeling submitted on October 16, 2009 for potential medication errors.

1.1 REGULATORY HISTORY

Vimpat (Lacosamide) Tablets and Injection were approved on October 28, 2008. The oral solution dosage form of Vimpat received a Complete Response on October 28, 2008. The Agency was concerned with the potential for dosing errors with the solution concentration (b) (4) and limitations (b) (4) (see OSE Review #2007-1610 dated May 15, 2008). We reviewed the labels and labeling for the oral solution in OSE Review #2008-633 dated May 15, 2008. The Applicant submitted a new concentration for the oral solution (10 mg/mL) and revised labels and labeling on October 16, 2009 in response to Complete Response letter.

1.2 PRODUCT INFORMATION

Vimpat tablets and oral solution are indicated for partial-onset seizures as adjunctive therapy in patients aged $\geq$ 17 years. The injection is indicated for short-term replacement when oral administration is not feasible in these patients. The recommended dose for partial onset seizures is 50 mg twice daily initially, then increased at weekly interval by increments of 100 mg per day, based on clinical response and tolerability, to 200 mg per day to 400 mg per day in two divided doses. When switching from oral to intravenous dose, the initial total daily intravenous dosage should equal the oral total daily dosage and frequency. The parenteral formulation of Vimpat can be administered without further dilution or may be mixed in a compatible diluent and should be administered intravenously over 30-60 minutes. Vimpat is available in tablets (50 mg, 100 mg, 150 mg, and 200 mg), solution for injection (200 mg/20 mL). The Applicant is proposing to add an oral solution (10 mg/mL) to the existing Vimpat product line.

2 METHODS AND MATERIALS

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS)

Because Vimpat Tablets and Injection are currently marketed products, DMEPA conducted a search of the FDA Adverse Event Reporting System (AERS) database on February 1, 2010 for any medication errors relevant to the labels or labeling of Vimpat using the following criteria: Active Ingredient "Lacosam%" and Trade Name "Vimpat%" and the MedDRA reaction terms "Medication Errors" (HGLT) and "Product Quality Issues" (HLGT).

The reports were manually reviewed to determine if medication errors occurred involving factors related to either labels or labeling. Those cases that did not describe a medication error, and those that were determined to be irrelevant, were excluded from further analysis.

2.2 PACKAGING, LABELS AND LABELING

DMEPA used Failure Mode and Effects Analysis (FMEA)[1] in our evaluation of the new concentration and revised container labels, carton and insert labeling submitted on October 16,

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2009 (see Appendices A and B). We also evaluated the recommendations pertaining to the previous labels and labeling in OSE Review #2008-633.

3 RESULTS

3.1 MEDICATION ERROR CASES

The AERS search retrieved a total of 9 reports involving Vimpat on February 1, 2010. However, none of these cases were related to issues concerning the labels or labeling of Vimpat. These cases involve suicide attempts, lack of efficacy, overdose (causality not given), and reports of tablet breaking per physicians' recommendations.

3.2 PACKAGING, LABELS AND LABELING

We compared the revised labels and labeling to the previously reviewed labels and labeling in OSE Review #2008-633 dated May 15, 2008. We note that our previous recommendations were incorporated in the revised labels and labeling.

4 DISCUSSION

4.1 VIMPAT ORAL SOLUTION NEW CONCENTRATION

Previously, the Applicant proposed a concentration (b) (4). We were concerned that this concentration could not measure the recommended dose in whole milliliter units. We were also concerned with the medication error potential of the Applicant's (b) (4) (see OSE Review #2007-1610). The new concentration addresses this concern since the new concentration allows for dosing in whole milliliter units (5 mL, 10 mL, 15 mL and 20 mL). This amount can be accurately measured with non-product specific measuring cups available in pharmacies. (b) (4). We concur with the Applicant that a specialized, drug-specific measuring dosing cup is not warranted.

5 CONCLUSIONS AND RECOMMENDATIONS

5.1 COMMENTS TO THE DIVISION

The new proposed concentration for Vimpat oral solution (10 mg/mL) and the revised labels and labeling submitted by the Applicant adequately addresses our previous concerns regarding the inability to measure the recommended dose in whole milliliter units. Additionally, the Applicant's revisions to the labels/labeling or the new concentration did not introduce any additional areas of vulnerability that could lead to medication errors.

We note that ONDQA had requested the addition of the total drug content/total volume in all labels and labeling. However, DMEPA disagreed and expressed concerns that such presentation might be confusing and could potentially lead to medication errors. After discussion, ONDQA agreed with DMEPA's recommendation to remove the statement of total drug content/total volume from all labels and labeling.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have any further questions or need clarifications, please contact Sarah Simon, OSE Project Manager, at 301-796-5205.

5.2 COMMENTS TO THE APPLICANT

We acknowledge the previous request from the Agency to add the total drug content/total volume to all labels and labeling. However, such presentation might be confusing and could potentially lead to medication errors. Thus, it should be deleted from all labels and labeling.

6 REFERENCES

1. Adverse Events Reporting System (AERS)

   AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post-marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

2. OSE Review #2007-1610 Proprietary Name, Label, and Labeling Review for Vimpat; Park, J.; May 15, 2008.

3. OSE Review #2008-633 Labels and Labeling Review for Vimpat; Park, J.; May 15, 2008.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22255	ORIG-1	SCHWARZ BIOSCIENCES INC	VIMPAT

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/s/

JUDY J PARK
04/07/2010

CARLOS M MENA-GRILLASCA
04/07/2010

DENISE P TOYER
04/07/2010

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:	May 15, 2008
To:	Russell Katz, MD, Director Division of Neurology Products Bob Rappaport, MD, Director Division of Anesthesia, Analgesia and Rheumatology Products
Thru:	Kellie Taylor, PharmD, MPH, Team Leader Denise Toyer, PharmD, Deputy Director Division of Medication Error Prevention
From:	Judy Park, PharmD, Safety Evaluator Division of Medication Error Prevention
Subject:	Labeling Review
Drug Name(s):	Vimpat (Lacosamide) Tablets, Oral Syrup, and Injection
Application Type/Number:	NDA 22-253, NDA 22-254, NDA 22-255, (b) (4)
Applicant:	Schwarz Biosciences, Inc.
OSE RCM #:	2008-633

CONTENTS

EXECUTIVE SUMMARY

The results of the Label and Labeling Risk Assessment found that the presentation of information and design of the proposed carton and container labels appears to be vulnerable to confusion that could lead to medication errors. The Division of Medication Error Prevention believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.2 that aim at reducing the risk of medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This consult was written in response to a request from the Division of Neurology to evaluate the container labels and carton labeling of Vimpat for its potential to contribute to medication errors. The proprietary name, Vimpat, and the insert labeling were evaluated under a separate review (OSE Review #2007-1611).

1.2 PRODUCT INFORMATION

Vimpat (Lacosamide) is a new molecular entity indicated for partial-onset seizures as adjunctive therapy in patients aged (b) (4) years and older, (b) (4) (b) (4). The recommended dose for partial onset seizures is 100 mg per day twice daily initially, then increased to 200 mg per day to 400 mg per day. (b) (4) The dose can be increased at weekly intervals by increments of 100 mg per day based on clinical response and tolerability. The maximum daily dosage of Vimpat is (b) (4) per day. When switching from oral to intravenous dose, the initial total daily intravenous dosage should equal the oral total daily dosage and frequency. The parenteral formulation of Vimpat can be administered without further dilution or may be mixed in a compatible diluent and should be administered intravenously over (b) (4). Vimpat will be available in 50 mg, 100 mg, 150 mg, 200 mg (b) (4) (b) (4) oral syrup, and 10 mg/mL solution for injection. (b) (4) For partial seizure indication, tablets, oral syrup and injectables are indicated.

2 METHODS AND MATERIALS

This section consists of two sections which describe the methods and materials used by the Division of Medication Error Prevention staff conducting a label, labeling, and/or packaging risk assessment. The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established

[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

Because our staff analyze reported misuse of drugs, our staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. We use FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted on April 9, 2008 following labels and labeling for our review (see Appendices A, B, C, D, E, F, and G for images):

- Retail Container for Injection: 10 mg/mL (20 mL vial)
- Retail Carton for Injection: 10 mg/mL (20 mL vial)
- Retail Container for Oral Syrup: (b) (4) 465 mL)
- Retail Carton for Oral Syrup: (b) (4) 465 mL)

(b) (4)

- Retail Container for Tablets : 50 mg, 100 mg, 150 mg, 200 mg (b) (4) (60, (b) (4) counts)

3 RESULTS

A review of the container labels and carton labeling identified several potential sources of medication error.

We noted a (b) (4) above the letter "A" of the proprietary name on the container labels and carton labeling. Additionally, the established name and dosage form appears smaller in size and prominence than the proprietary name while the company logo is similar in prominence as the proprietary name.

The retail labels and labeling for all strengths of tablets have the same trade dress except for the strength colors. The differentiating strength colors for 50 mg, 100 mg, and 150 mg tablets look almost identical since they are presented in similar shades of pastel and are bordered in black.

For the injectable dosage form, we noted the total drug content (200 mg/20 mL) and the concentration (10 mg/mL) of the injectable have the same prominence. Additionally, the container label for the injectable does not list the inactive ingredients qualitatively and quantitatively and the carton labeling does not list the quantitative amount of the inactive ingredients.

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

(b) (4)

Lastly, the precautionary statement for Phenylketonurics on oral syrup label (b) (4) is confusing because it is unclear (b) (4) (b) (4).

4 DISCUSSION

The results of the Label and Labeling Risk Assessment found that the presentation of information and design of the proposed container labels and carton labeling appears to be vulnerable to confusion that could lead to medication errors.

We noted inadequate differentiation among the proposed product strengths of the tablet formulation. The visual similarities of the container labels and carton labeling can lead to product selection errors because all strengths are usually stocked side-by-side on a pharmacy shelf. We are concerned with the similar strength colors of the 50 mg, 100 mg, and 150 mg tablets, in addition to identical trade dress for all strengths. The minimal differences in the strength color may not afford adequate differentiation of the product strengths.

Per 21 CFR 201.10(g)(2), the established name should be at least ½ the size of the proprietary name and have the prominence commensurate with the prominence of the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. The proposed labels do not present the established name in accordance with the regulations.

We noted the use of (b) (4) on the container labels and carton labeling. This is distracting and draws attention away from important product information such as drug name and product strength. The (b) (4) contributes to the overall visual similarity of the labels. The company logo should also be diminished in size and color since it competes with other important information such as the drug name and strength.

The same prominence of the total drug content (200 mg/20 mL) and the concentration (10 mg/mL) of the injectable makes it difficult to identify the total drug content. The differences between total drug content and concentration would be more evident if the concentration is presented under the total drug content and has less prominence.

Additionally, the injectable container label does not list the inactive ingredients qualitatively and quantitatively and the carton labeling does not list the quantitative amount of the inactive ingredients as it should per 21 CFR 201.100(b)(5).

(b) (4)

Lastly, the precautionary statement for Phenylketonurics on oral syrup is confusing because it is unclear (b) (4).

5 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed container labels and carton labeling introduces vulnerability to confusion that could lead to medication errors. We believe the risks we have identified can be

addressed and mitigated prior to drug approval, and provides recommendations in Section 5.2 that aim at reducing the risk of medication errors.

5.1 COMMENTS TO THE DIVISION

Based upon our assessment of the labels and labeling, we have identified areas needed of improvement. We have provided recommendations in Section 5.2 and request this information be forwarded to the Applicant.

We would appreciate feedback on the final outcome of this review. Please copy us on any communication to the Applicant with regard to this review. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Daniel Brounstein, Project Manager, at 301-796-0674.

5.2 COMMENTS TO THE APPLICANT

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed container labels and carton labeling introduces vulnerability to confusion that could lead to medication errors. The Division of Medication Error Prevention believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations below that aim at reducing the risk of medication errors.

Overall, our Risk Assessment is limited by our current understanding of medication errors and causality. The successful application of Failure Modes and Effect Analysis depends upon the learning gained for a spontaneous reporting program. It is quite possible that our understanding of medication error causality would benefit from unreported medication errors; and, that this understanding could have enabled the Staff to identify vulnerability in the proposed name, packaging, and labeling that was not identified in this assessment. To help minimize this limitation in future assessments, we encourage the Applicant to provide the Agency with medication error reports involving their marketed drug products regardless of adverse event severity.

5.2.1 General Comment

1. We recommend removing (b) (4) above the proprietary name on all container labels and carton labeling.
2. Per 21 CFR 201.10(g)(2), ensure that the established name is the same font size as the dosage form and at least ½ the size of the proprietary name, and have the prominence commensurate with the prominence of the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
3. Decrease the prominence of the company logo in size and color so that it does not compete with other important information such as the drug name and strength.

5.2.2 Tablets

1. The current proposed presentation of the labels lack adequate differentiation since all the labels have the same trade dress. Although we recognize that the strength color correlates to the tablet colors, the proposed strength colors on labels for 50 mg, 100 mg and 150 mg look particularly similar to one another because they are presented in similar pastel colors and bordered in black. Provide additional visual differentiation of the labels so that each strength is clearly differentiated from the remainder of the strengths.

2. (b) (4) [redacted]

5.2.3 Oral Syrup

1. Revise the precautionary warning statement for Phenylketonurics (b) (4) [redacted] (b) (4) [redacted]

5.2.4 Injectable

1. Increase the prominence of the total drug content (200 mg/20 mL). Relocate the concentration (10 mg/mL) to below the total drug content.

3 Pages of Draft Labeling have been Withheld in Full Immediately Following this Page as B4 (CCI/TS)

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/s/

Judy Park
5/15/2008 10:11:10 AM
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