CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-006

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

Pre-Decisional Agency Information

Date: June 10, 2009

To: Russell Katz, M.D., Division Director
Division of Neurology Products

CC: Tamy Kim, PharmD, Regulatory Project Manager
Division of Neurology Products

Mary Dempsey, Project Management Officer
OSE – Division of Risk Management

Sharon R. Mills, BSN, RN, CCRP, Patient Product Information Reviewer
OSE – Division of Risk Management

Jodi Duckhorn, M.A., Team Leader
OSE – Division of Risk Management

From: Sharon Watson, PharmD, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications

Subject: Sabril (vigabatrin) Tablets, NDA: 20-427
Sabril (vigabatrin) for Oral Solution, NDA: 22-006

DDMAC has reviewed the proposed Medication Guide (Med Guide) for Sabril Tablets and Oral Solution as edited in the June 5, 2009, review from OSE's Division of Risk Management. We agree with OSE's comments and offer the following in addition. Please also refer to DDMAC's April 21, 2009, emailed review of the proposed Med Guide for Sabril Tablets. If you have any questions or concerns regarding these comments, please contact me.

GENERAL

(b)(4)

4 Page(s) of Draft Labeling has been Withheld in Full after this page as B4 (CCI/TS)

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/s/

Sharon Watson
6/10/2009 11:22:50 AM
DDMAC CONSUMER REVIEWER

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 6, 2009
To:	Russell Katz, M.D. Director, Division of Neurology Products, HFD-120
Through:	Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis, HFD-420
From:	Tselaine Jones Smith, Pharm.D., Safety Evaluator Kristina C. Arnwine, Pharm.D., Team Leader Denise Toyer, Pharm.D., Deputy Director Division of Medication Error Prevention and Analysis, HFD-420
Subject:	Label, Labeling and Product Packaging Review
Drug Name(s):	Sabril (Vigabatrin for Oral Solution) 500 mg
Application Type/Number:	NDA 20-427 NDA 22-006
Applicant/applicant:	Ovation Pharmaceuticals, Inc.
OSE RCM #:	2008-73

***** This document contains proprietary and confidential information that should not be released to the public.*****

CONTENTS

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Neurology Products (DNP, HFD-120) to evaluate the labels and labeling for Sabril Tablets (NDA 20-427) and Sabril for Oral Solution (NDA 22-006). DMEPA is also conducting a re-review of the proprietary name prior to approval of this NDA and the results will be forthcoming in OSE Review # 2008-73. Additionally, OSE/DRISK will address the Risk Evaluation and Mitigation Strategy (REMS) separately (OSE Review # 2008-1903).

The Division of Medication Error Prevention and Analysis provided comments previously (OSE Reviews #05-0520-1, 2006-603 and 2006-757) on Sabril Tablets labels and labeling. Additionally, we have had ongoing discussions with DNP about safety concerns with Sabril for Oral Solution (i.e., the dosage form, product strength, dosing devices and the lack of information on how to reconstitute, dose and administer the product) and its labels/labeling.

1.2 REGULATORY HISTORY

In OSE Review #2006-603 and 2006-757, DMEPA reviewed the proprietary name for Sabril Tablets and Sabril for Oral Solution. We also provided comments on the draft labels and labeling for both products. DMEPA found the proprietary name Sabril acceptable for both dosage forms.

Subsequently, during the pre-action proprietary name and label/labeling review DMEPA identified safety concerns with Sabril for Oral Solution (i.e., the dosage form, product strength, dosing devices and the lack of information on how to reconstitute, dose and administer the product). DMEPA believed these safety concerns could lead to confusion and medication errors. On August 14, 2008, we met with DNP to discuss these safety concerns.

DNP concurred with DMEPA's concerns and subsequently, on September 19, 2008 a teleconference was held to discuss these safety concerns with the Applicant and to discuss the six foreign medication error cases for Sabril for Oral Solution submitted by the Applicant. Subsequently, on September 28, 2008 the Applicant provided three strategies to ensure accurate dosing with vigabatrin solution and prevent medication errors. These included supplying patients/caregivers with the appropriate dosing devices (two sets of 3 mL and 10 mL oral syringes (b) (4)), providing educational tools which include (b) (4) a 'Dosing Instruction Sheet for Patients/Caregivers' and revising language on their proposed foil packets.

On December 10, 2008, DMEPA met with DNP to discuss the September submissions. Both DNP and DMEPA agreed with the Applicant's decision not to reformulate or manufacture multiple strengths of the product. However, DMEPA continued to have safety concerns with regard to the proposed dosing devices, educational tools, and the 'Dosing Instruction Sheet for Patients/Caregivers.'

To address DMEPA's concerns, a teleconference was held between DNP, DMEPA and the Applicant on January 21, 2009. The Applicant agreed to conduct a usability study on their dosing devices and on the presentation of information in the instructions for use. The Applicant also provided clear details of their distribution process. Based on each individual prescription, a specialty pharmacy will repackage the drug product and dispense the appropriate quantity, instructions for use, and the dosing devices to the end-user.

1.3 PRODUCT INFORMATION

Sabril (vigabatrin) is available in two dosage forms (tablets and oral solution) for two different indications of use. Sabril tablets are indicated as adjunctive therapy for adult patients with refractory complex partial seizures who have inadequately responded to alternative treatments and for whom the potential benefits outweigh the potential risk of developing the peripheral Field Vision Defect. The recommended dose for refractory complex partial seizures in adults is to initiate therapy of the at 500 mg tablets twice daily with or without food. The total daily dose may be increased in 500 mg weekly intervals depending on the response. The usual effective dose of Sabril in adults is 3 grams/day (1.5 grams twice daily).

Sabril for Oral Solution is indicated as a monotherapy for pediatric patients (birth up to 2 years of age) with Infantile Spasms for whom the potential benefits outweigh the potential risk of developing the peripheral Field Vision Defect. The recommended dose for infantile spasms is 50 mg/kg/day (1 ml/kg/day) given in two divided doses and can be titrated by 25 mg/kg to 50 mg/kg increments every three days up to 150 mg/kg/day. The entire contents of the packet of powder should be emptied into a container and using a calibrated 10 mL syringe dissolved in 10 mL of liquid (water, milk or infant formula). The final concentration is 50 mg/mL.

2 METHODS AND MATERIALS

This section describes the methods and materials used by DMEPA staff to conduct a label, labeling, and/or packaging risk assessment. The primary focus of the assessments is to identify and remedy potential sources of medication errors prior to drug approval. We define 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. [3]

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 the proprietary and established name, strength, form, container quantity, expiration date, and so on. The insert labeling is intended to communicate to practitioners all the 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.[4]

For this product the Applicant submitted labels, labeling and other pertinent documents on the following dates: (See Appendices A through E)

March 1, 2007- Sabril Tablets (NDA #20-427)

- Physician Sample Container Label (6 count)
- Container Label (100 count)

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

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

- Carton Labeling

December 10, 2007 -Sabril for Oral Solution (NDA #22-006)

- Carton Labeling

September 10, 2008 - Sabril for Oral Solution (NDA #22-006)

- Assessment of Six Medication Errors

September 28, 2008 - Sabril for Oral Solution (NDA #22-006)

- Container Labels-Samples A and B
- Dosing Instruction Sheet for Patients/Caregiver
- (b) (4)

January 30, 2009

- Insert Labeling for Sabril Tablets and Sabril for Oral Solution

March 10, 2009

- Safety and Readability Evaluation of Sabril Powder Mixing and Administration Instructions
- 3 mL and 10 mL Oral Syringes Dose Accuracy and Durability Testing Summary Report
- Medication Guide for Sabril Tablets and Sabril for Oral Solution
- Instructions on How to Mix and Administer Sabril for Oral Solution

3 RESULTS AND DISCUSSION

DMEPA has been working with DNP and the Applicant to address the issues we raised with respect to the measuring devices and the instructions for use for Sabril for Oral Solution (i.e. the Dosing Instruction Sheet, (b) (4) and the Medication Guide for Sabril for Oral Solution). See Appendix F for results.

The latest submission (March 10, 2009) contained the results of the requested usability studies on the dosing devices and on the presentation of information in the instructions for use. The study's objectives were appropriate to assess a patient's ability to understand and execute the instructions; in order to minimize patient safety issues and the risk of medication errors (e.g., when using the instructions for use and dosing devices).

The Applicant used an outside consultant, (b) (4); to help them evaluate and revise their instructions for use. (b) (4) Subsequently, the Applicant conducted several rounds of testing; involving 21 participants where participants were asked to read and execute the instructions. After round one (10 participants) the Applicant revised the instructions for use based upon the feedback received from ten participants. In round two (11 participants) the Applicant used the revised instructions from round one. After the first four participants, the Applicant noted only two of those four completed the instructions successfully. At that time, the Applicant revised the instructions to include one minor change. Consequently the remaining seven participants successfully mixed and administered the medication. Thus, the study results demonstrate that participants can understand and execute the instructions using the appropriate size syringes at three different dosing levels.

(b) (4)

Although, the revised instructions for use addressed our concerns in Appendix F, we note that the Applicant did not provide specific instructions (e.g., remove the plunger) for cleaning the dosing devices.

In addition, we note that the Applicant failed to include the appropriate liquid temperature (i.e. cold or room temperature) for mixing the product. The Applicant has performed stability testing of Sabril for Oral Solution using cold (refrigerated) and room temperature liquid and has not provided any stability data to support mixing the product using warm or hot liquid. Highlighting the temperature of the liquid (i.e. **cold or room temperature** liquid) will ensure that the correct temperature of liquid is used for mixing.

Additionally, we noted the following areas of needed improvement with respect to the Sabril's labels and labeling and Medication Guide Statements for both the tablets and oral solution.

3.1 SABRIL FOR ORAL SOLUTION

3.1.1 Container Labels and Carton Labeling

The listed dosing instructions on the container labels and carton labeling are not complete when compared to the Instructions for Preparing and Giving your Baby Sabril Sheet. As currently presented, caregivers may administer the entire contents of the packet rather than the prescribed dose and/or save or reuse left over drug product. Revising the 'instructions for use' statement to read 'see the package insert for full prescribing information' in accordance with 21 CFR 201.55 will help address this concern.

3.1.2 Insert Labeling

The proposed proprietary name (Sabril and Sabril for Oral Solution), established name (Vigabatrin and Vigabatrin for Oral Solution), and dosage form (for Oral Solution and Powder for Oral Solution) appear inconsistently. As previously communicated in our July 10, 2006 correspondence to the Applicant, the established name should read as '(Vigabatrin) for Oral Solution.' Additionally, in accordance with the *CDER Data Standards Manual* the dosage form should read 'for oral solution' without reference to 'powder'. Finally, the proprietary name should appear as 'Sabril,' which is consistent with numerous correspondences between DNP and the Applicant.

3.2 MEDICATION GUIDE STATEMENT FOR LABELS AND LABELING FOR SABRIL TABLETS AND SABRIL FOR ORAL SOLUTION

(b) (4)

4 RECOMMENDATIONS

We request the following recommendations be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy us on any communication to the applicant with regard to this review. If you have further questions or need clarifications, please contact Daniel Brounstein, project manager, at 301-796-0674.

4.1 COMMENTS TO THE APPLICANT

Based on assessment of the container label, carton and insert labeling and the Instructions for Preparing and Giving your Baby Sabril for Oral Solution and the Medication Guides for Sabril Tablets and Sabril for Oral Solution, we have the following recommendations.

A. Sabril for Oral Solution

1. Container Labels and Carton Labeling

   a. Revise the 'directions for use' statement to read 'see the package insert for full prescribing information' in accordance with 21 CFR 201.55.

   b. We concur with your proposal to bold the statement 'immediately administer directed amount and discard unused portion' as presented in Sample B of your September 28, 2008 submission.

2. Insert Labeling

   a. The proprietary name is inconsistently presented throughout (e.g., Full Prescribing Information: (1.1) Indications and Usage and (2.1) Dosage and Administration sections). Revise the proprietary name to read Sabril throughout the insert labeling.

   b. The dosage form is inconsistently presented throughout (e.g., Highlights of Prescribing Information: Dosage Form and Strengths Section). Revise the dosage form to read 'for Oral Solution'.

3. Instructions for Preparing and Giving your Baby Sabril

   a. Provide detailed instructions for cleaning the dosing devices.

   b. Highlight the temperature of the liquid that should be used for mixing the product (i.e. **cold or room temperature** liquid).

B. Medication Guides for Sabril Tablets and Sabril for Oral Solution

   1. Medication Guide Statement

      a) Although your labels and labeling contain the required statement alerting the dispenser to provide the Medication Guide with the product for all strengths and formulations, we recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

         i. "Dispense the enclosed Medication Guide to each patient." Or,

         ii."Dispense the accompanying Medication Guide to each patient."

   2. Distribution of Medication Guides to the Specialty Pharmacies and to Patients

      a) Sufficient numbers of Medication Guides should be provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each "usual" or average dose. For example:

         i. A minimum of two Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 2 tablets daily, thus a monthly supply is 30 tablets.

         ii. A minimum of one Medication Guide would be provided with unit of use bottle or carton where it is expected that all tablets or packets would be supplied to the patient.

5 REFERENCES

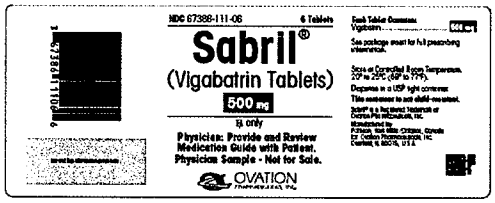
5.1 REVIEW OF SAFETY APPLICATIONS

OSE Review # 05-0250 and 05-0250-1 dated November 21, 2005

OSE Review # 2006-603 and 2006-757 dated November 9, 2006

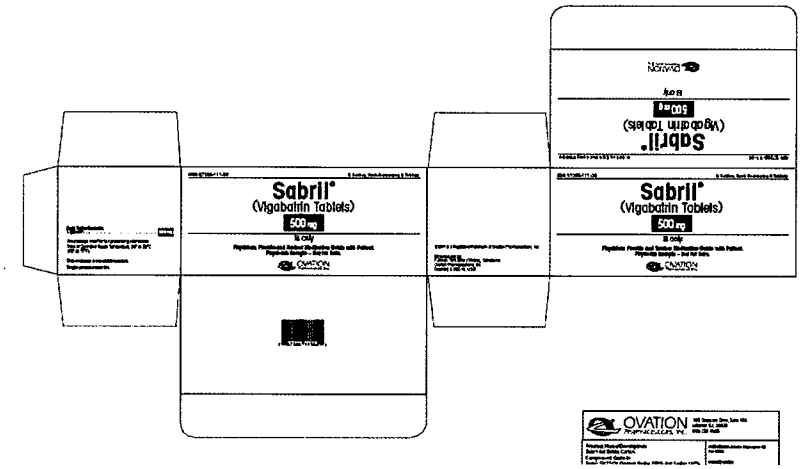
6 APPENDICES

Appendix A: Sample Container Label for Sabril Tablets – 6 count (Note: Images not to scale)



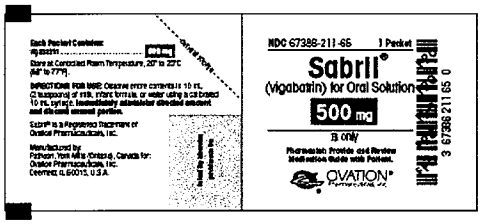
Appendix B: Container Label for Sabril Tablets – 100 count (Note: Images not to scale)

Appendix C: Carton Labeling for Sabril Tablets (Note: Images not to scale)



Appendix D: Container Label for Sabril for Oral Solution (Note: Images not to scale)

Sample B



Appendix E: Carton Labeling for Sabril for Oral Solution (Note: Images not to scale)

Appendix F:

RESULTS

A. LABEL, LABELING AND PRODUCT PACKAGING RISK ASSESSMENT

The Division of Medication Error Prevention and Analysis' deficiencies noted following our Label, Labeling and Packaging Risk Assessment of the labels and labeling submitted by the Applicant on December 28, 2007, September 28, 2008 and January 30, 2009.

B. Container Labels and Carton Labeling for Sabril for Oral Solution

The statements 'Unused portions should be discarded' and 'Do not to save and reuse leftover liquid' lack prominence.

C. Insert Labeling for Sabril for Oral Solution

1. Instructions are not available on what to do with leftover solution.
2. The Dosage and Administration Section lacks a dosing table for infants.
3. The dosing table for neonates is confusing.
4. Under Section 2.1, the statement '...up to a maximum 150 mg/day' does not correlate with the defined maximum dose range (100 mg/kg/day to 150 mg/day) in the neonate dosing table.
6. Under Section 17.4 (FDA-approved Medication Guide):
    - Section 4 lacks vital information on the reconstitution, dosing and administration of Sabril for Oral Solution.
    - The presentation of information on the proper techniques used to reconstitute, measure the dose and administer the product is incomplete.
    - The following statement in Section 4 is confusing: "Use an oral syringe or other dosing device to measure the 10 mL volume and give your child the appropriate amount of this medicine, using an oral syringe to measure the exact volume".

D. Dosing devices (b) (4), 10 mL and 3 mL Oral Syringes)

a. Oral Syringes

Providing two different size oral syringes (3 mL and 10 mL) may lead to confusion and lead to inappropriate dosing of the drug product.

(b) (4)

E. Packaging Configuration

Less than or more than one packet may be required to achieve recommended doses.

F. Instructions for Use for Sabril for Oral Solution

1. Medication Guide

a. Section 4 lacks vital information on the reconstitution, dosing and administration of Sabril for Oral Solution.

b. The presentation of information on the proper techniques used to reconstitute, measure the dose and administer the product is incomplete.

c. The following statement in Section 4 is confusing: "Use an oral syringe or other dosing device to measure the 10 mL volume and give your child the appropriate amount of this medicine, using an oral syringe to measure the exact volume".

2. Dosing Instruction Sheet for Patients/Caregivers

a. The 'Instructions for making Sabril for liquid solution for Sabril Powder' do not correlate with the instructions for use in the medication guide.

b. The 'Instructions for making Sabril for liquid solution for Sabril Powder' are incomplete and lack vital steps that are important in the reconstitution, dosing and administration of this product. For example, the instructions:

- lack a description of what items should be available in order to prepare the drug (i.e. the number of packets needed, water for reconstitution, the dosing cup and oral syringes, etc.)
- do not state how to remove the drug product from the packets,
- do not state how to get 10 mL of water into the syringe,
- in Step 4 are confusing due to the order in which they appear,
- do not warn caregivers not to mix drug product with large volumes of liquid (i.e. addition of prepared product to bottles and cups already filled with liquid),
- do not instruct caregivers on what device to use to administer the product

c. The 'Sabril Dosing Instructions' has dosing only up to 14 days.

(b) (4)

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/s/

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