

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-006

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

**U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of New Drugs, OND I
Division of Neurology Products**

NDA/BLA #s: 20427, 22006
Products: Sabril Tablets and Sabril for Oral Solution (Vigabatrin)
SPONSOR: Ovation Pharmaceuticals, Inc.
FROM: Robert Temple, M.D.
DATE: August 20, 2009

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a 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.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for Sabril to ensure that the benefits of the drug outweigh the risks of vision loss and of suicidal thoughts and behaviors. In reaching this determination, we considered the following:

- A. It is not possible to determine precisely the size of the population likely to use Sabril. Approximately 1% of the adult population in the US has a seizure disorder. Adults with complex partial seizures account for approximately 60% of the adults with epilepsy in the United States.¹ Sabril would be indicated for patients with complex partial seizures who have failed to respond adequately to several alternative treatments. It is estimated that 40% of patients with complex

¹ Wallin, MT and Krutzke JF. Neuroepidemiology. Chapter 43. In Neurology in Clinical Practice, 4th Edition. Editors: Bradley WG, Daroff, RB, Fenichel GM, and Jankovic J. Elsevier 2004, Philadelphia.

partial seizures have intractable seizures not satisfactory treated by currently available drugs.²

It is estimated that infantile spasms, for which no other approved treatment is available, affect approximately 1 out of 4,000 to 6,000 live births,³ or approximately 1000 infants born in the United States each year.⁴

- B. Patients with epilepsy have approximately two to three times the risk of death from any cause compared with persons without epilepsy. 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, or the underlying condition resulting in seizures.

The long term prognosis of infantile spasms is bleak. Fewer than 5% of patients are neurodevelopmentally normal. While there are no definitive data that treatment of the spasms will improve long term neurologic prognosis, there are limited data suggesting that this is the case.

- C. The efficacy of Sabril for the treatment of complex partial seizures in adults was studied in two placebo-controlled trials. In these trials, approximately 45% of patients randomized to Sabril (3 g/day) experienced a 50% or greater reduction in seizure frequency, compared to approximately 15% of patients randomized to placebo.

The efficacy of Sabril for infantile spasms was evaluated in two multicenter trials. In Study 1A, patients were randomized to receive either low-dose (18-36 mg/kg/day, n=114) or high-dose (100-148 mg/kg/day, n=107) vigabatrin. Seventeen patients in the high dose group achieved spasm freedom (the primary endpoint) compared with 8 patients in the low dose group. This difference was statistically significant (p=0.0375). Study W019 (N=40) was a multicenter, randomized, double-blind, placebo-controlled, parallel group trial consisting of a pre-treatment (baseline) period of 2-3 days, followed by a 5-day double-blind treatment phase during which patients were treated with vigabatrin or placebo. Over a 24 hour period, a statistically significant (p=0.03) difference in the overall percentage of reductions in spasms between the vigabatrin group (68.9%) and the placebo group (17.0%) was observed.

- D. If approved for complex partial seizures in adults, treatment with Sabril would be chronic in patients for whom it is effective. If approved for infantile spasms, treatment with Sabril is expected to be for up to 2 years in patients who show clinical benefit. Patients in these two seizure populations who do not exhibit

² Sander JW. The epidemiology of Epilepsy Revisited. *Curr Opin Neurol* 2003; 16:165-170.

³ Mackay MT, et al. *Neurology* 2004; 62:1668-1681.

⁴ In 2005, a total of 4,138,349 births were registered in the United States. From National Vital Statistics Reports. 2007; 56 (6).

benefit would be exposed to only a brief trial of the medication (approximately 2 weeks to 3 months).

E. Known serious risks of Sabril include vision loss and suicidal thoughts and behavior.

In adults, Sabril causes progressive permanent bilateral concentric vision loss in 30 percent or more of patients. Vision loss can range in severity from mild to severe, including tunnel vision to within about 10 degrees of visual fixation, which can result in disability. It also appears that close monitoring can limit damage in many (but not all) cases; therefore, periodic visual field testing is critical. Sabril can sometimes damage the central retina and may decrease visual acuity; therefore, visual acuity also needs to be monitored. The time to onset of vision loss from Sabril is unpredictable. It can occur within weeks of starting treatment or may occur long after treatment begins, even after months or years. Monitoring throughout use is therefore essential.

Permanent vision loss may also occur in infants and children treated with Sabril, but assessing visual field defects is especially difficult in children, and the frequency and extent of vision loss in infants and children is poorly characterized. In infants and children, vision loss may not be detected until it is severe. Nonetheless, monitoring vision in this population is also essential and should be done to the extent possible at baseline and during therapy.

An increased risk of suicidal thoughts and behavior is an expected serious risk of Sabril. This risk appears to be shared by antiepileptic drugs as a therapeutic class and was demonstrated in a meta-analysis of randomized, parallel-arm, placebo-controlled clinical trial data for 11 AEDs.⁵ In the 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, was shared by drugs with varying mechanisms of action, and was observed for all indications studied, suggesting that the risk applies to all antiepileptic drugs regardless of indication of use.

F. Sabril is a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Sabril. FDA has determined that Sabril 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 Sabril.

⁵Statistical review and evaluation: Antiepileptic drugs and suicidality. (Accessed September 24, 2008, at <http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4372b1-01-FDA.pdf>.)

FDA has determined that Sabril is a product that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use, or continue to use, Sabril. FDA has also determined that Sabril is a product for which patient labeling could help prevent serious adverse events.

The elements of the REMS will include a Medication Guide, a Communication Plan, elements to assure safe use (including the following: healthcare providers who prescribe Sabril have particular training or experience, or are specially certified; pharmacies, practitioners, or healthcare settings that dispense Sabril are specially certified; Sabril may be dispensed to patients only with evidence or other documentation of safe-use conditions; each patient using Sabril will be subject to certain monitoring; and each patient using Sabril be enrolled in a registry), and a timetable for submission of assessments of the REMS.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22006	ORIG 1	OVATION PHARMACEUTICALS INC	SABRIL (VIGABATRIN)
NDA 22006	ORIG 1	OVATION PHARMACEUTICALS INC	SABRIL (VIGABATRIN)
NDA 22006	ORIG 1	OVATION PHARMACEUTICALS INC	SABRIL (VIGABATRIN)
NDA 22006	ORIG 1	OVATION PHARMACEUTICALS INC	SABRIL (VIGABATRIN)
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NDA 22006	ORIG 1	OVATION PHARMACEUTICALS INC	SABRIL (VIGABATRIN)
NDA 22006	ORIG 1	OVATION PHARMACEUTICALS INC	SABRIL (VIGABATRIN)
NDA 22006	ORIG 1	OVATION PHARMACEUTICALS INC	SABRIL (VIGABATRIN)
NDA 22006	ORIG 1	OVATION PHARMACEUTICALS INC	SABRIL (VIGABATRIN)
NDA 22006	ORIG 1	OVATION PHARMACEUTICALS INC	SABRIL (VIGABATRIN)

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/s/

TAMY E KIM
08/20/2009

ROBERT TEMPLE
08/20/2009



**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: July 16, 2009

To: Russell Katz, M.D., Director
Division of Neurology Products (DNP), HFD-120

Thru: Claudia Karwoski, Pharm.D., Director
Division of Risk Management (DRISK)
Office of Surveillance and Epidemiology (OSE)

From: OSE Vigabatrin REMS Review Team:

Marcia Britt, Ph.D., Health Education Reviewer, DRISK
Mary Dempsey, Risk Management Program Coordinator, DRISK
Jodi Duckhorn, M.A., Lead Social Science Analyst, DRISK
Brian Gordon, M.A., Social Science Reviewer, DRISK
Joyce Weaver, Pharm.D., Senior Drug Risk Management Analyst, DRISK,
Scientific Lead

Subject: Review of Risk Evaluation and Mitigation Strategy (REMS)

Drug Name(s): Sabril (vigabatrin)

Application Type/
Number: 20-427 (Complex Partial Seizures), 22-006 (Infantile Spasms)

Applicant/sponsor
: Lundbeck, Inc

OSE RCM #: 2008-1903

Title OSE Safety Review

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1 INTRODUCTION AND BACKGROUND

Vigabatrin is an enzyme-activated irreversible inhibitor of Gamma-aminobutyric acid (GABA)-transaminase, an enzyme responsible for the catabolism of the inhibitory neurotransmitter GABA. Vigabatrin increases GABA concentrations in the brain, thereby enhancing GABA-mediated neurotransmission. Vigabatrin has not been approved for marketing in the U.S., but applications for the treatment of infantile spasms and complex partial seizures are pending with the FDA.

Vigabatrin was first approved for marketing in 1989 in the United Kingdom, with other approvals occurring subsequently in many other regulatory jurisdictions. Currently, vigabatrin is authorized in the European Union through a Mutual Recognition Procedure. In Europe, vigabatrin is approved as second-line treatment for resistant partial epilepsies, with or without secondary generalization, and for the management of infantile spasms. In 1998, after about a decade of use in Europe, a role of vigabatrin in causing defects in peripheral vision became known. The Committee for Proprietary Medicinal Products (CPMP) recommended that marketing authorization be maintained with strengthened labeling. Prescribing is limited to neurologists and other physicians with experience in the treatment of epilepsy.

The Agency has taken two previous actions on vigabatrin. The first, an approvable action for the use of vigabatrin to treat complex partial seizures, was issued in November 1997. Subsequent to this approvable action, information emerged regarding the visual adverse effects of vigabatrin. In October 1998, the Agency believed that the evidence relating to vision toxicity tipped the risk-benefit balance such that the application was not approvable.

A meeting of the Peripheral and Central Nervous System Drugs Advisory Committee was held on January 6 and 7, 2009 to obtain advice from a panel of experts regarding the pending applications. The committee members voted unanimously that the applications should be approved. The committee believed that for both indications, a risk evaluation and mitigation strategy (REMS) should be utilized. For patients receiving vigabatrin for complex partial seizures, periodic mandatory vision assessment should be a component of the REMS.

2 MATERIAL REVIEWED

The following Sabril submissions, all available in the EDR, were reviewed.

- Proposed REMS and REMS Supporting Document, received November 26, 2008;
- Proposed REMS and REMS Supporting Document, received December 24, 2008;
- Proposed REMS and REMS Supporting Document, received January 30, 2009;
- Proposed REMS and REMS Supporting Document, received February 24, 2009;
- Proposed REMS and REMS Supporting Document, received April 9, 2009; and
- Proposed REMS and REMS Supporting Document, received July 7, 2009.

3 RESULTS OF REVIEW OF PROPOSED REMS

3.1 GOALS

The goals of the REMS are:

- 1) To reduce the risk of a Sabril-induced vision loss while delivering benefit to the appropriate patient populations;
- 2) To ensure that all patients receive a baseline ophthalmologic evaluation; 50% of patients will receive within 2 weeks of starting Sabril and 100% within 4 weeks;
- 3) To discontinue Sabril therapy in patients who experience an inadequate clinical response;
- 4) To detect Sabril-induced vision loss as early as possible;
- 5) To ensure regular vision monitoring to facilitate ongoing benefit-risk assessments;
and
- 6) To inform patients/parent or legal guardian of the serious risks associated with Sabril, including vision loss and increased risk of suicidal thoughts and behavior.

3.2 REMS ELEMENTS

The Sabril REMS is comprised of a Medication Guide, a Communication Plan, Elements to Assure Safe Use, an Implementation System, a Timetable for Assessment, and a Patient Registry.

3.2.1 MEDICATION GUIDE

The approved Medication Guide will be dispensed with each Sabril prescription in accordance with 21 CFR 208.24.

3.2.2 COMMUNICATION PLAN

At product launch and periodically thereafter Lundbeck will send a Dear Healthcare Professional Letter via direct mail to all registered ophthalmologists. The Sabril package insert will accompany the letter. Additionally, Lundbeck Inc. field representatives will call on neuro-ophthalmologists and/or ophthalmologists at key epilepsy centers at product launch to disseminate the Sabril package inserts.

3.2.3 ELEMENTS TO ASSURE SAFE USE

- 1) Healthcare providers who prescribe Sabril are specially certified.
 - a) Prescribers must be enrolled in the REMS program and attest to their understanding of the REMS program requirements and the risks associated with Sabril. Prescribers commit to the following:
 - i) Reading the full prescribing information (PI) and Medication Guide;
 - ii) Having knowledge of the approved indications for Sabril;
 - iii) Having experience in treating epilepsy;

- iv) Having knowledge of the risks of Sabril, especially vision loss;
 - v) If prescribing for infantile spasms, having knowledge of the risk of MRI abnormalities with use of Sabril;
 - vi) Assessing the effectiveness of Sabril within 2-4 weeks in infants infantile spasms and within 12 weeks in adults; in the case that insufficient clinical benefit has occurred, Sabril will be discontinued;
 - vii) Ordering and reviewing visual assessment at the time of initiation of Sabril (with the baseline assessment to be conducted within 4 weeks of starting Sabril), and every 3 months after initiating Sabril therapy;
 - viii) Educating patients on the risks and benefits of Sabril;
 - ix) Enrolling patients in the REMS program;
 - x) Reviewing the Sabril Medication Guide with every patient;
 - xi) Counseling the patient if the patient is not complying with the required vision assessment, and removing the patient from therapy if the patient still fails to comply with required vision assessment; and
 - xii) Reporting to the Sponsor or to the FDA any serious adverse events with Sabril.
- 2) Pharmacies that dispense Sabril are certified by Lundbeck Inc.
- a) Certified pharmacies will ship Sabril only to patients who are enrolled in the REMS program, and whose continued eligibility has been established within the REMS.
 - b) The pharmacies will be notified by the REMS coordinating center (SHARE [Support Help And Resources for Epilepsy] Call Center) about patient eligibility to receive Sabril, including continued use after the assessment period, and loss of eligibility based on non-compliance with visual monitoring.
 - c) Lundbeck Inc will ensure that a designated representative of each certified pharmacy:
 - i) is trained on the REMS program;
 - ii) trains pharmacy staff on the REMS program procedures and REMS materials as described above prior to dispensing Sabril; and
 - iii) agrees that the certified pharmacy may be audited by the FDA, Lundbeck Inc, or a third party designated by Lundbeck Inc.
- 3) Each patient treated with Sabril must be enrolled in the Sabril REMS
- a) To enroll in the REMS, each patient or parent/legal guardian must sign a patient enrollment form indicating that:
 - i) they have read the Medication Guide;
 - ii) the prescriber has explained the risk of visual loss;
 - iii) vision loss, should it occur, is irreversible;
 - iv) periodic vision assessment, although not protective from all vision loss, is required for the duration of therapy, and even after stopping Sabril; and

- v) response to Sabril will be assessed after a short trial period (3 months for complex partial seizures and 1 month for infantile spasms); should the patient's response to Sabril be insufficient, therapy with Sabril will be stopped
- 4) Sabril is dispensed to patients with evidence or other documentation of safe-use conditions
 - a) Patient vision will be tested at baseline (within 4 weeks of starting Sabril), every 3 months while on Sabril, and after therapy with Sabril has stopped; the results of the exam will be reported on the Ophthalmologic Assessment Form
 - b) Prior to entering maintenance therapy, response to treatment with seizures must be assessed; response to treatment with Sabril for seizures will be assessed within 3 months of initiating therapy and for infantile spasms within 1 month; meaningful improvement must be documented, or Sabril must be discontinued.
 - 5) Each patient using the drug is enrolled in a registry
 - a) The registry will collect prescriber specialty, patient demographics, diagnosis, prior and concurrent anti-seizure medications, periodic ophthalmologic assessment data (i.e., the results of every 3-month monitoring), and the proportion of patients receiving Sabril for refractory complex partial seizures and infantile spasms patients who respond/do not respond to Sabril during the treatment initiation phase.

3.2.4 Implementation System

The Implementation System includes the following:

- 1) Lundbeck Inc will maintain a database capturing certified pharmacies, the REMS coordinating center (SHARE Call Center), and enrolled patients.
- 2) Lundbeck Inc will monitor distribution data to ensure that only certified pharmacies are distributing and dispensing Tracleer.
- 3) Lundbeck Inc. will train and audit both the REMS coordinating center and the certified pharmacies on a regular basis.
- 4) Lundbeck Inc will ensure that, prior to the certified pharmacy dispensing the first Sabril prescription, a completed and signed Treatment Initiation Form is completed for each enrolled patient and received by the REMS coordinating center.
- 5) Lundbeck Inc will ensure that, prior to the certified pharmacy dispensing Sabril for the maintenance phase of therapy, the Treatment Maintenance Form is completed for each enrolled patient and received by the REMS coordinating center.
- 6) Lundbeck Inc will ensure that the Ophthalmologic Assessment Form is received for all registered patients at 3-month intervals (plus a 90-day grace period). These forms will be reconciled against a list of all registered patients to assess adherence to Sabril REMS requirements.
- 7) Lundbeck Inc will ensure that patients who do not comply with the vision monitoring requirements of the REMS are tapered from Sabril.

3.2.5 TIMETABLE FOR SUBMISSION OF ASSESSMENTS

REMS assessments will be submitted to the FDA every 6 months for 1 year, and then yearly thereafter. The assessment period will close no earlier than 60 days prior to the date the respective assessment is due. The assessment is to be received by the FDA on the due date.

3.3 PROPOSED REMS ASSESSMENT PLAN

Information needed for assessment is not a required element of the REMS. However, this information should be addressed in the REMS approval letter and discussed in the REMS Supporting Document.

REMS Assessment reports will include the following information.

- 1) Registration and drug distribution data
 - a) Report of Sabril distribution;
 - b) The number of patients registered for the reporting period and cumulatively, including the age and gender of the patients;
 - c) The number and specialties of prescribers registered for the reporting period and cumulatively;
 - d) The number of patients who discontinue Sabril therapy before the beginning of the maintenance phase;
 - e) The number of patients whose therapy is interrupted due to changing prescribers.
 - f) The number of prescribers who are de-registered and reasons;
 - g) The number of prescribers who are re-registered and reasons;
 - h) The number of patients who are de-registered and reasons;
 - i) The number of Sabril shipments to patients without prior authorization from Lundbeck Inc.; and
 - j) The number of pharmacies who are de-enrolled, with reasons for de-enrollment.
- 2) Medication Guide distribution data
 - a) Number of Medication Guides dispensed in comparison to the number of prescriptions shipped during the reporting period.
 - b) A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
 - c) A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
- 3) Report of mandatory benefit-risk assessments prior to entering maintenance therapy, including how many patients completed the mandatory benefit-risk assessment, and how many patients did not complete the mandatory benefit-risk assessment.
- 4) Vision Monitoring

- a) Frequency distribution of number of reminder calls for vision monitoring made per patient;
 - b) Review of pattern of reminder calls to confirm no gap in therapy;
 - c) The number of patients who miss vision monitoring appointments, the reason they miss them, and how long the monitoring is delayed;
 - d) The number and percent of patients who obtain baseline vision monitoring within the first 2 weeks and within the first 4 weeks of treatment initiation, age, and prescriber;
 - e) The number and percent of patients who do not obtain baseline vision monitoring within the first 4 weeks after treatment initiation, by reason, age, and prescriber;
 - f) The number of patients who are at least 60 days late in obtaining required vision monitoring appointments on 3 separate occasions;
 - g) The number of patients by age who do not complete the required vision monitoring within the REMS assessment period;
 - h) The number of patients who are exempted from vision monitoring by reason checked on the Ophthalmologic Assessment Form and by prescriber;
 - i) Narrative summary and analysis of information collected on Ophthalmologic Assessment Forms; and
 - j) Narrative summary and assessments of reports of vision loss.
- 5) Patient/Parent or Legal Guardian Knowledge, Attitude and Behavior (KAB) Surveys
- a) Number of patients, parents, and legal guardians who call to volunteer for survey participation;
 - b) Number of patients who meet inclusion criteria;
 - c) Description of survey participants;
 - i) Indication for Sabril use;
 - ii) Duration of use (as indicated in SHARE database);
 - iii) Gender;
 - iv) Age;
 - v) Geographic region;
 - vi) Status (patient, parent, legal guardian); and
 - vii) Where treated.
 - d) Frequency distribution of responses to each question; that is, the number of respondents who give each answer to each question;
 - e) Percent of those answering each response to each question in total and separately for patients and caregivers;
 - f) Percent of respondents indicating correct response to each objective in total and separately for patients and caregivers;
 - g) Analyses will be stratified by indication for Sabril use as well as analyses for the combined sample;
 - h) Level of understanding of Sabril risks as measured by the score on the KAB survey;

- i) Number and percent of respondents in patient/parent/legal guardian KAB survey who report reading the Medication Guide; and
 - j) Number and percent of respondents in the patient/parent/legal guardian KAB survey who report they receive a Medication Guide with each prescription.
- 6) Ophthalmic professional KAB Surveys
- a) The number of ophthalmic professionals in the sample, in total, and by key characteristics;
 - b) The number of ophthalmic professionals attempted to contact at each wave; of those attempted to contact:
 - i) number who opt out/ask to be removed from list;
 - ii) number who agree to participate in the survey;
 - iii) Of those who agree to participate, number who qualify;
 - iv) Of those who qualify, number who complete any portion of the interview; and
 - v) Of those who qualify, number who complete the survey.
 - c) Description of survey participants
 - i) Experience with Sabril; and
 - ii) Geographic region.
 - d) Frequency distribution of responses to each question;
 - e) Percent of those answering each response to each question; and
 - f) Percent of respondents indicating correct response to each objective.
- 7) Prescriber KAB Surveys
- a) The number of physicians in the sample, in total, and by key characteristics;
 - b) The number of physicians attempted to contact at each wave; of those attempted to contact:
 - i) Number who opt out/ask to be removed from list;
 - ii) Number who agree to participate in the survey;
 - iii) Of those who agree to participate, number who qualify;
 - iv) Of those who qualify, number who complete any portion of the interview;
 - v) Of those who qualify, number who complete the survey;
 - vi) Description of survey participants;
 - (1) Medical specialty & whether adult or pediatric practice;
 - (2) Experience with Sabril; and
 - (3) Geographic region.
 - vii) Frequency distribution of responses to each question;
 - viii) Percent of those answering each response to each question; and
 - ix) Percent of respondents indicating correct response to each objective; and
 - c) Additional analyses, included subset by adult or pediatric practice, if needed.

- 8) With respect to REMS goals, an assessment of the extent to which the elements to assure safe use are meeting the goals or whether the goals or such elements should be modified.

4 DISCUSSION/RECOMMENDATIONS

The Sponsor has appropriately responded to all Agency comments. The REMS should be approved. We note that the proposed REMS and REMS Supporting Document submitted by the Sponsor require editing to comply with the format currently being used by the Agency. The reformatted REMS document and the REMS Supporting Document are appended. We understand additional formatting revisions may be necessary as this REMS goes through the final clearance process.

4.1 RECOMMENDATIONS FOR DNP

The Information needed for assessment (REMS Assessment Plan) should include but is not limited to the following data. This information should be addressed in the REMS approval letter:

REMS Assessment reports will include the following information.

- 1) Registration and drug distribution data
 - a) Report of Sabril distribution;
 - b) The number of patients registered for the reporting period and cumulatively, including the age and gender of the patients;
 - c) The number and specialties of prescribers registered for the reporting period and cumulatively;
 - d) The number of patients who discontinue Sabril therapy before the beginning of the maintenance phase;
 - e) The number of patients whose therapy is interrupted due to changing prescribers.
 - f) The number of prescribers who are de-registered and reasons;
 - g) The number of prescribers who are re-registered and reasons;
 - h) The number of patients who are de-registered and reasons;
 - i) The number of Sabril shipments to patients without prior authorization from Lundbeck Inc.; and
 - j) The number of pharmacies who are de-enrolled, with reasons for de-enrollment.
- 2) Medication Guide distribution data
 - a) Number of Medication Guides dispensed in comparison to the number of prescriptions shipped during the reporting period.
 - b) A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24

- c) A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
- 3) Report of mandatory benefit-risk assessments prior to entering maintenance therapy, including how many patients completed the mandatory benefit-risk assessment, and how many patients did not complete the mandatory benefit-risk assessment.
- 4) Vision Monitoring
- a) Frequency distribution of number of reminder calls for vision monitoring made per patient;
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 - c) The number of patients who miss vision monitoring appointments, the reason they miss them, and how long the monitoring is delayed;
 - d) The number and percent of patients who obtain baseline vision monitoring within the first 2 weeks and within the first 4 weeks of treatment initiation, age, and prescriber;
 - e) The number and percent of patients who do not obtain baseline vision monitoring within the first 4 weeks after treatment initiation, by reason, age, and prescriber;
 - f) The number of patients who are at least 60 days late in obtaining required vision monitoring appointments on 3 separate occasions;
 - g) The number of patients by age who do not complete the required vision monitoring within the REMS assessment period;
 - h) The number of patients who are exempted from vision monitoring by reason checked on the Ophthalmologic Assessment Form and by prescriber;
 - i) Narrative summary and analysis of information collected on Ophthalmologic Assessment Forms; and
 - j) Narrative summary and assessments of reports of vision loss.
- 5) Patient/Parent or Legal Guardian Knowledge, Attitude and Behavior (KAB) Surveys
- a) Number of patients, parents, and legal guardians who call to volunteer for survey participation;
 - b) Number of patients who meet inclusion criteria;
 - c) Description of survey participants;
 - i) Indication for Sabril use;
 - ii) Duration of use (as indicated in SHARE database);
 - iii) Gender;
 - iv) Age;
 - v) Geographic region;
 - vi) Status (patient, parent, legal guardian); and
 - vii) Where treated.
 - d) Frequency distribution of responses to each question; that is, the number of respondents who give each answer to each question;

- e) Percent of those answering each response to each question in total and separately for patients and caregivers;
 - f) Percent of respondents indicating correct response to each objective in total and separately for patients and caregivers;
 - g) Analyses will be stratified by indication for Sabril use as well as analyses for the combined sample;
 - h) Level of understanding of Sabril risks as measured by the score on the KAB survey;
 - i) Number and percent of respondents in patient/parent/legal guardian KAB survey who report reading the Medication Guide; and
 - j) Number and percent of respondents in the patient/parent/legal guardian KAB survey who report they receive a Medication Guide with each prescription.
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 - iv) Of those who qualify, number who complete any portion of the interview; and
 - v) Of those who qualify, number who complete the survey.
 - c) Description of survey participants
 - i) Experience with Sabril; and
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 - e) Percent of those answering each response to each question; and
 - f) Percent of respondents indicating correct response to each objective.
- 7) Prescriber KAB Surveys
- a) The number of physicians in the sample, in total, and by key characteristics;
 - b) The number of physicians attempted to contact at each wave; of those attempted to contact:
 - i) Number who opt out/ask to be removed from list;
 - ii) Number who agree to participate in the survey;
 - iii) Of those who agree to participate, number who qualify;
 - iv) Of those who qualify, number who complete any portion of the interview;
 - v) Of those who qualify, number who complete the survey;
 - vi) Description of survey participants;
 - (1) Medical specialty & whether adult or pediatric practice;

- (2) Experience with Sabril; and
 - (3) Geographic region.
 - vii) Frequency distribution of responses to each question;
 - viii) Percent of those answering each response to each question; and
 - ix) Percent of respondents indicating correct response to each objective; and
 - c) Additional analyses, included subset by adult or pediatric practice, if needed.
- 8) With respect to REMS goals, an assessment of the extent to which the elements to assure safe use are meeting the goals or whether the goals or such elements should be modified.

4.2 RECOMMENDATIONS FOR THE SPONSOR

Please refer to the REMS and the REMS Supporting Document which include the recommended changes.

APPENDICES

Appendix I—REMS document

RISK EVALUATION & MITIGATION STRATEGY (REMS)

Title:	Risk Evaluation & Mitigation Strategy (REMS)
Product Name:	Sabril (vigabatrin) NDAs 20-427, 22-006
Sponsor:	Lundbeck Inc. Four Parkway North Deerfield, Illinois 60015 Jenny Swalec, Sr. Director, Global Regulatory Affairs 847-282-1066
Date:	15 July 2009

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

The goals of the REMS are:

- 1) To reduce the risk of a Sabril-induced vision loss while delivering benefit to the appropriate patient populations;
- 2) To ensure that all patients receive a baseline ophthalmologic evaluation; 50% of patients will receive within 2 weeks of starting Sabril and 100% within 4 weeks;
- 3) To discontinue Sabril therapy in patients who experience an inadequate clinical response;
- 4) To detect Sabril-induced vision loss as early as possible;
- 5) To ensure regular vision monitoring to facilitate ongoing benefit-risk assessments; and
- 6) To inform patients/parent or legal guardian of the serious risks associated with Sabril, including vision loss and increased risk of suicidal thoughts and behavior.

II. REMS ELEMENTS

A. Medication Guide

Lundbeck will ensure that a Medication Guide is dispensed with each 30-day supply of Sabril and in accordance with 21CFR 208.24. The Medication Guide will be included in the Sabril Starter Kit to be reviewed with the patient/parent or legal guardian by the physician prior to starting the patient on Sabril therapy. The Medication Guide will also be provided to patients by the certified pharmacies which each prescription.

Please see appended Medication Guide.

B. Elements To Assure Safe Use

- 1) Healthcare providers who prescribe Sabril are specially certified under 505-1 (f)(3)(A).
 - a) Lundbeck Inc. will ensure that prescribers are enrolled in the REMS program and attest to their understanding of the REMS program requirements and the risks associated with Sabril. Lundbeck Inc. will ensure that prescribers commit to the following:
 - i) Reading the full prescribing information (PI) and Medication Guide;
 - ii) Having knowledge of the approved indications for Sabril;
 - iii) Having experience in treating epilepsy;
 - iv) Having knowledge of the risks of Sabril, especially vision loss;
 - v) If prescribing for infantile spasms, having knowledge of the risk of MRI abnormalities with use of Sabril;
 - vi) Assessing the effectiveness of Sabril within 2-4 weeks in infants and within 12 weeks in adults; in the case that insufficient clinical benefit has occurred, Sabril will be discontinued;
 - vii) Ordering and reviewing visual assessment at the time of initiation of Sabril (with the baseline assessment to be conducted within 4 weeks of starting Sabril), and every 3 months after initiating Sabril therapy;
 - viii) Educating patients on the risks and benefits of Sabril;
 - ix) Enrolling patients in the REMS program;
 - x) Reviewing the Sabril Medication Guide with every patient;
 - xi) Counseling the patient if the patient is not complying with the required vision monitoring beyond the baseline test, and removing the patient from therapy if the patient still fails to comply with required vision monitoring; and
 - xii) Reporting to the Sponsor at 1-800-455-1141 any serious adverse events with Sabril and provide all known details of the event.
 - b) The prescriber may exempt certain patients from vision assessment, using the Ophthalmic Assessment form, if:

- i) The patient is blind
- ii) The patient's general neurological condition precludes the need for visual assessment
- iii) The patient's medical condition prevents visual assessment being performed safely, documented by the prescriber.
- iv) For other reasons documented by the prescriber
- c) The following materials are part of the REMS and are appended
 - (1) Dear Healthcare Professional (HCP) Letter
 - (2) Dear HCP Medication Taper Letter
 - (3) Prescriber Enrollment and Agreement Form
 - (4) Treatment Initiation Form
 - (5) Treatment Maintenance Form
 - (6) Ophthalmologic Assessment Form
 - (7) Patient-Physician agreement- Refractory CPS
 - (8) Parent/Legal Guardian –Physician Agreement-IS

Lundbeck Inc. will maintain a database of certified prescribers in the REMS program. Lundbeck Inc. will ensure that prescribers comply with the requirements of the REMS and may de-enroll noncompliant prescribers.

- 2) Pharmacies that dispense Sabril are specially certified by Lundbeck Inc under 505-1(f)(3)(B).
 - a) Lundbeck Inc will ensure that to be certified, each pharmacy designates a representative who:
 - i) is trained on the REMS program, including;
 - (1) Each certified pharmacy ships Sabril only to patients who are enrolled in the REMS program, and whose continued eligibility has been established within the REMS.
 - (2) Each certified pharmacy obtains treatment forms and prescriptions only from the REMS coordinating center.
 - (3) Each certified pharmacy obtains a dispense authorization from the REMS coordinating center before dispensing the first Sabril prescription and before dispensing each monthly refill.
 - ii) trains pharmacy staff on the REMS program procedures and REMS materials for dispensing
 - iii) agrees that the certified pharmacy may be audited by the FDA, Lundbeck Inc, or a third party designated by Lundbeck Inc.

- 3) Sabril is dispensed to patients with evidence or other documentation of safe-use conditions under 505-1(f)(3)(D):
- a) Lundbeck Inc. will ensure that each patient treated with Sabril is enrolled in the Sabril REMS before Sabril is dispensed to him or her. Lundbeck Inc. will ensure that, to become enrolled, each patient or parent/legal guardian must sign a patient enrollment form indicating that:
 - i) they have read the Medication Guide;
 - ii) the prescriber has explained the risk of visual loss;
 - iii) vision loss, should it occur, is irreversible;
 - iv) that prescribed vision assessments must be obtained
 - v) periodic vision assessment, although not protective from all vision loss, is required for the duration of therapy, and even after stopping Sabril; and
 - vi) response to Sabril will be assessed after a short trial period (3 months for complex partial seizures and 1 month for infantile spasms); should the patient's response to Sabril be insufficient, therapy with Sabril will be stopped
 - b) The following materials are part of the REMS and are appended
 - (1) Patient-Physician agreement- Refractory CPS
 - (2) Parent/Legal Guardian –Physician Agreement-IS
 - (3) Seizure Diary
 - (4) Sabril Reconstitution and Dosing Instructions (Powder for Oral Solution)
 - (5) Starter Kit
 - (6) Treatment Maintenance Form
 - (7) Ophthalmologic Assessment Form
- 4) Each patient using the drug is enrolled in a registry under 505-1(f)(3)(F)
The registry will collect prescriber specialty, patient demographics, diagnosis, prior and concurrent anti-seizure medications, periodic ophthalmologic assessment data (i.e., the results of every 3-month monitoring), and the proportion of patients receiving Sabril for

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The Implementation System includes the following. Lundbeck Inc. will:

- 1) maintain a validated and secured (21 CFR Part 11 compliant) database of certified pharmacies, enrolled prescribers and enrolled patients.

- 2) monitor distribution data to ensure that only certified pharmacies are distributing and dispensing Sabril.
- 3) train all personnel working for the REMS coordinating center (TheraCom) directly responsible for the Sabril REMS program and site managers at all certified pharmacies. Lundbeck Inc. will audit all certified pharmacies and the REMS coordinating center on an annual basis.
- 4) ensure that the REMS coordinating center receives each enrolled patient's completed Treatment Maintenance Form documenting an assessment of risk-benefit prior to authorizing the maintenance phase of therapy.
- 5) ensure that the REMS coordinating center obtains the completed Ophthalmologic Assessment Form for all registered patients at 3-month intervals (plus a 90-day grace period) prior to authorizing continued dispensing of monthly refills
- 6) ensure that certified pharmacies dispense Sabril only if they receive authorization for each dispense from the REMS coordinating center (SHARE [Support Help And Resources for Epilepsy] Call Center).
- 7) ensure that patients who do not comply with the vision monitoring requirements of the REMS are tapered from Sabril.
- 8) monitor and evaluate the implementation of the elements provided for under Sections B.1, B.2, B.3, and B.4, above, in the manner described in the REMS supporting document, and take reasonable steps to work to improve implementation of these elements.

E. Timetable for Submission of Assessments

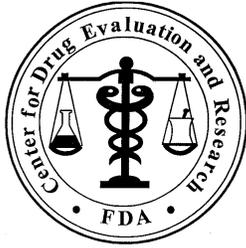
REMS assessments will be submitted to the FDA every 6 months from the date of approval of the REMS for 1 year, and then annually thereafter. The assessment period will close no earlier than 60 days prior to the date the respective assessment is due. The assessment is to be received by the FDA on the due date.

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Mary Dempsey
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DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski
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DRUG SAFETY OFFICE 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: June 5, 2009

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

Through: Jodi Duckhorn, M.A., Team Leader
Division of Risk Management (DRISK)

From: Sharon R. Mills, BSN, RN, CCRP
Patient Product Information Reviewer
Division of Risk Management (DRISK)

Subject: DRISK Review of Patient Labeling (Medication Guide and Instructions for Use)

Drug Name(s):

- SABRIL (vigabatrin) Tablets, NDA 20-427
- SABRIL (vigabatrin) for Oral Solution, NDA 22-006

Applicant/sponsor: Ovation Pharmaceuticals, Inc.

OSE RCM #: 2008-1903

1 INTRODUCTION

This review is written in response to a request from the Division of Neurology Products (DNP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) and Instructions for Use. The Medication Guide is one element of a Risk Evaluation and Mitigation Strategy (REMS) for SABRIL. The applicant submitted proposed REMS for SABRIL on November 26, 2009 and amended the REMS on February 24, 2009, March 10, 2009, and April 9, 2009. The applicant's proposed REMS is currently under review by DRISK. That review will be provided to DNP under separate cover.

The agency has taken two previous actions on SABRIL (vigabatrin) Tablets: an Approvable action in November 1997 and a Not Approvable action in October 1998.

2 MATERIAL REVIEWED

- SABRIL (vigabatrin) Tablets Prescribing Information (PI) submitted March 1, 2007, amended by the applicant and further revised by DNP throughout the current review cycle, and provided to DRISK on May 21, 2009.
- SABRIL (vigabatrin) for Oral Solution Prescribing Information (PI) submitted March 8, 2007, amended by the applicant and further revised by DNP throughout the review cycle. We reviewed the PI provided by DNP to DRISK on May 21, 2009 and the DNP eRoom version dated May 27, 2009.
- Combined draft SABRIL (vigabatrin) Tablets and SABRIL (vigabatrin) for Oral Solution Medication Guide (MG) provided by the review division on May 8, 2009 based on the individual SABRIL (vigabatrin) Tablets MG submitted by the applicant on March 1, 2009 and revised throughout the review cycle, and the proposed SABRIL (vigabatrin) for Oral Solution MG submitted by the applicant on March 8, 2007, and revised throughout the review cycle.

3 DISCUSSION



(b) (4)

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DNP's draft combined MG and IFU has a Flesch Kincaid grade level of 8.5 and a Flesch Reading Ease score of 58.2%. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). Our MG and IFU revisions have an improved Flesch Kinkaid grade level of 7.1 and a Flesch Reading Ease score of 72.1%.

In our review of the MG and IFU, we have:

- simplified wording and clarified concepts where possible,
- ensured that the MG and IFU are consistent with the PI,
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the MG document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are **bolded, underlined and italicized**.

We are providing the review division a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG.

4 CONCLUSIONS AND RECOMMENDATIONS

We have the following comments on the Medication Guide:

1. The name of the MG should reflect the name of the product, not the indication. We concur with DDMAC's "General" Comment and have revised the MG accordingly.
2. The applicant uses both the term "doctor" and "healthcare provider" in the MG. We recommend using one term consistently throughout the MG, except in the required verbatim statement at the end of the section "What are the possible side effects of TRADENAME?" where the term "doctor" is required.
3. In the section "What is the most important information I should know about SABRIL?"
 - Given that 30% or more patients experience loss of vision that is progressive and permanent, DNP should consider whether "some patients" is an accurate description, and revise accordingly.
 - We defer to DNP to address the DDMAC comment regarding whether "blurry vision" is sufficient to describe the risk of damage to the central retina.

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/s/

Sharon Mills
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DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
6/7/2009 08:33:36 PM
DRUG SAFETY OFFICE 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: July 11, 2008

To: FDA Peripheral and Central Nervous System Drugs Advisory Committee

Through: Gerald Dal Pan, M.D., M.H.S., Director
Office of Surveillance and Epidemiology (OSE)

From: OSE Sabril Risk Evaluation and Mitigation Strategy Review Team:
Scientific Lead: Joyce Weaver, Pharm.D., Senior Risk Management Analyst, Division of Risk Management (DRISK)

Team Members:
Suzanne Berkman, Pharm.D., Acting Team Leader, DRISK
Mary Dempsey, Risk Management Coordinator, DRISK
Claudia Karwoski, Pharm.D., Acting Division Director, DRISK

Subject: Review of Risk Management Proposal

Drug Name(s): Sabril (vigabatrin)

Application Type/Number: 20-427 (Complex Partial Seizures), 22-006 (Infantile Spasms)

Applicant/sponsor: Ovation Pharmaceuticals

1 INTRODUCTION AND BACKGROUND

Vigabatrin is an enzyme-activated irreversible inhibitor of Gamma-aminobutyric acid (GABA)-transaminase, an enzyme responsible for the catabolism of the inhibitory neurotransmitter GABA. Vigabatrin increases GABA concentrations in the brain, thereby enhancing GABA-mediated neurotransmission. Vigabatrin has not been approved for marketing in the U.S., but applications for the treatment of infantile spasms and complex partial seizures are pending with the FDA.

Vigabatrin was first approved for marketing in 1989 in the United Kingdom, with other approvals occurring subsequently in many other jurisdictions. Currently, vigabatrin is authorized in the European Union through a Mutual Recognition Procedure. In Europe, vigabatrin is approved as second-line treatment for resistant partial epilepsies, with or without secondary generalization, and for the management of infantile spasms. In 1998, after about a decade of use in Europe, a role of vigabatrin in causing defects in peripheral vision became known. The Committee for Proprietary Medicinal Products (CPMP) recommended that marketing authorization be maintained with strengthened labeling. Prescribing is limited to neurologists and other physicians with experience in the treatment of epilepsy.

Data presented in the Sponsor's Periodic Safety Update Reports for vigabatrin indicate that the worldwide exposure to vigabatrin in commercial marketing has been about 970,000 patient-years.¹ About 975 cases of visual field defect have been spontaneously reported during commercial marketing.

The Agency has taken two previous actions on vigabatrin. The first, an approvable action for the use of vigabatrin to treat complex partial seizures, was issued in November 1997. Subsequent to this approvable action, information emerged regarding the visual adverse effects of vigabatrin. In October 1998, the Agency believed that the evidence relating to vision toxicity tipped the risk-benefit balance such that the application was not approvable. FDA requested additional information characterizing the visual effects of vigabatrin, including information addressing if a rational monitoring protocol could be expected to prevent loss of vision in patients taking vigabatrin. Based on the draft review of Dr. Ronald Farkas, there remains doubt that such a monitoring protocol is possible.

Intramyelinic edema (IME), a second serious safety issue for vigabatrin, was first noted in animal models, and subsequently was observed in infants receiving vigabatrin. A retrospective epidemiological study of patients with infantile spasms confirmed previous reports linking the use of vigabatrin with IME.

¹ Exposure data calculated by the Sponsor for marketing through September 2007, and based on an assumption of average daily dose; data presented to NDA.

2 SUMMARY OF PROPOSED RISK MITIGATION MEASURES FOR VIGABATRIN

In December 2007 Ovation Pharmaceuticals submitted a proposed Risk Management Plan for vigabatrin for use in infantile spasms and complex partial seizures. The plan addresses the risk of vision loss associated with vigabatrin, but does not address IME.

Proposed Labeling

The proposed labeling presents the risk of vision loss in a boxed warning. The *Warnings and Precautions* section sets out the following monitoring protocols: for patients receiving vigabatrin for infantile spasms, ophthalmologic testing would be performed at baseline, every 3 months for the first 18 months of treatment, and then every 6 months thereafter; for patients receiving vigabatrin for partial complex seizures, ophthalmologic testing would be performed at baseline and then every 6 months thereafter. The method of testing is not specified.

Development of IME is included as a warning in the proposed labeling; however, the proposed labeling provides no guidance to prescribers on whether pediatric patients receiving vigabatrin should be monitored for IME. The proposed labeling states that periodic monitoring with magnetic resonance imaging (MRI) is not needed for adults receiving vigabatrin.

The sponsor also proposes a Medication Guide.

In addition, the proposed Risk Management Plan² comprises the following components:

Physician Attestation

To prescribe vigabatrin, prescribers must receive education about the risks of vigabatrin, and they must attest that they understand the risks and the monitoring protocol.

Product Distribution via Specialty Pharmacies

Product distribution would be accomplished via specialty pharmacies only when prescribed by prescribers who have received education and who have attested as described above.

Implementation

All prescriptions for vigabatrin must be cleared through the Share Central Call Center, the Sponsor's organizational unit that implements the program. The prescription would be processed only after the physician's education and attestation are confirmed.

Patient-Physician Agreement

The patient-physician agreement provides education regarding the risks of vigabatrin, and provides a structured approach to consider the benefits and risks of vigabatrin after a period of use. After a 12-week period of therapy the patient and physician agree to

² Ovation Pharmaceuticals Proposed Risk Management Plan for Vigabatrin, dated December 14, 2007; submitted to the NDA.

consider the whether the product is effective for the individual patient. This agreement is not monitored by or shared with the Sponsor or the Agency; therefore, this would be entirely voluntary.

Evaluation of Risk Mitigation Measures

The program would be evaluated based on patient/caretaker and prescriber surveys, and evaluation of data from the Specialty Pharmacies. The proposal does not explain how the Specialty Pharmacies would gather this data (e.g., compliance with monitoring of visual field).

Pharmacovigilance

The Sponsor proposes routine pharmacovigilance to monitor product safety.

3 RISK TO VISION WITH USE OF VIGABATRIN

It is not clear that the risks of vigabatrin to the vision of patients using the product can be sufficiently mitigated; that is, that the degree of visual field loss can be limited to one that is justified by the benefits of the drug. Dr. Farkas' draft ophthalmic safety review raises the following issues important to the potential to mitigate the risks of vigabatrin:

1. Onset of visual defect may occur very early in some patients, and there is no reliable evidence for a "safe" period of exposure (for example, during the 12-week effectiveness evaluation period proposed by the Sponsor in the risk mitigation protocol);
2. Loss of visual field may progress in some patients even after long periods of apparent stability in the visual field;
3. Progression to severe visual field defect may occur in a sudden, unpredictable manner, even after a long period of apparent stability in the field; given this fact, establishing a rational monitoring interval is problematic;
4. There are not uniform, highly sensitive screening tools that can ensure accurate assessment of visual field defects; the use of perimetry or electroretinography cannot ensure the early detection of mild-to-moderate damage to visual field; the electroretinogram (ERG), a test that does not require patients to be highly cooperative, is not a useful tool to detect early or mild-to-moderate visual field defects; tests that require extensive cooperation (e.g., visual field tests) can also have a learning effect, and are not suitable for many patients (e.g., the very young).
5. Visual field testing should be repeated to increase the likelihood that the test results are reliable, but repeat testing delays diagnosis of a visual field defect;
6. Monitoring of visual fields in very young or cognitively impaired children is especially challenging;
7. Visual defect might progress in some patients even after discontinuation of vigabatrin; and

8. Should patients experience a clinically significant loss of visual field with vigabatrin, a number of these patients most assuredly will be rendered blind eventually as they experience loss of central vision that occurs commonly with age, for example, with age-related macular degeneration.

4 RISK OF IME WITH USE OF VIGABATRIN

A retrospective epidemiological study of patients with infantile spasms confirmed previous reports linking the use of vigabatrin with IME. In the study, lesions consistent with IME were present in 21.5% of vigabatrin-exposed patients, compared with 4.1% in the patients who had not received vigabatrin ($p < 0.001$). This study also supported previous observations that the MRI abnormalities are transient in most cases, and they are more likely to be found in infants exposed to high doses of vigabatrin (defined as 125 mg per kg of body weight per day). Evidence so far suggests that IME occurs in infants, but perhaps not in adults exposed to vigabatrin. An age presumed to be safe from the development of IME remains undefined. The clinical significance of the lesions is not clear. Dr. Philip Sheridan, the Medical Officer in the Division of Neurology Products who reviewed this issue, recommended that, should vigabatrin be approved for the treatment of infantile spasms, patients receiving vigabatrin should be followed with periodic MRIs.

5 DISCUSSION

We note that the Sponsor has not yet submitted full details of the risk mitigation proposal. However, the proposal submitted raises the following issues that should be discussed during the August 6, 2008 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee.

Considering the issues regarding product safety and visual field monitoring raised in Dr. Farkas' review, is there any risk mitigation strategy that could mitigate the product risks sufficiently?

Although monitoring of visual fields and prompt discontinuation of vigabatrin in patients in whom a visual field defect is found will spare some patients from further loss of vision, it is likely that visual field defect, including severe defect, will occur in some patients regardless of the monitoring regimen that is implemented. Is there a patient population for which the risk-benefit profile of vigabatrin acceptable? Is there a monitoring regimen that would render the risk-benefit profile of vigabatrin acceptable? We would appreciate advice on the specific protocol (type of testing, interval between testing, findings that would warrant discontinuation of the drug, and length of follow-up after drug discontinuation) from the Advisory Committee.

Is monitoring with periodic MRIs a workable solution to mitigate the risk of IME?

Do we fully understand the conditions under which IME develops? If not, should this issue be resolved prior to making vigabatrin available for commercial use? Is it practical to expect patients to undergo periodic MRI monitoring? We note that this might require sedation of infants (which is not without risk) who would be unable to cooperate with the study otherwise.

If vigabatrin is approved with a Risk Evaluation and Mitigation Strategy, should the strategy link monitoring of visual field and monitoring with MRIs to access to vigabatrin?

The Sponsor's proposal asks only that the prescriber understand the risks to vision. A commitment to following a monitoring protocol for vision loss or IME is not included. Furthermore, access to vigabatrin is not contingent on follow a monitoring protocol. Given the severity of the risks, this linkage between monitoring and drug access might be advisable, and should be discussed by the advisory committee.

6 CONCLUSION

The Sponsor submitted a risk mitigation proposal to mitigate the risk of loss of vision with the use of vigabatrin. The primary methods proposed to mitigate the risk of loss of vision are prescriber education and attestation of an understanding of the risks of vigabatrin, and distribution of vigabatrin through Specialty Pharmacies. The full role of the Specialty Pharmacies within the plan is not explained in the proposal. The proposal envisages that the Specialty Pharmacies will collect data on the monitoring of visual fields (the specifics of this collection are not explained), but the proposal does not link the visual field monitoring to access to the drug.

Given the issues raised in Dr. Farkas' review, we are not confident that the risks of vigabatrin can be sufficiently mitigated for patients; that is, it is not clear that the degree of visual field loss can be limited to one that is justified by the benefits of the drug. However, should such a program be attempted, we would suggest that consideration be given to linking access to vigabatrin with required safety monitoring.

Neither the proposed labeling nor the plan fully addressed the risk of IME. The clinical significance of this risk needs to be fully addressed to determine an approach to mitigate this risk. We are concerned that a monitoring protocol to mitigate the risk of IME via mandated periodic monitoring with MRI could place a large and perhaps unworkable burden on patients and their caretakers. This should be considered only if the expected benefits of vigabatrin outweigh its risks.

The details of the committee's discussion will be considered in the final design of the risk mitigation program, should one or both of the pending applications for vigabatrin be approved. We look forward to the committee's advice regarding whether periodic visual testing might sufficiently mitigate the risks to vision of vigabatrin, and, if so, what monitoring protocols might be appropriate for adults and for children. Likewise, we look forward to the committee's advice regarding whether periodic monitoring with MRIs is a workable approach to mitigate the risk of IME.

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Mary Dempsey
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DRUG SAFETY OFFICE REVIEWER

Gerald DalPan
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MEDICAL OFFICER