

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-427

**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 20427	ORIG 1	OVATION PHARMACEUTICALS INC	SABRIL (VIGABATRIN) TABLET 500MG
NDA 20427	ORIG 1	OVATION PHARMACEUTICALS INC	SABRIL (VIGABATRIN) TABLET 500MG
NDA 20427	ORIG 1	OVATION PHARMACEUTICALS INC	SABRIL (VIGABATRIN) TABLET 500MG
NDA 20427	ORIG 1	OVATION PHARMACEUTICALS INC	SABRIL (VIGABATRIN) TABLET 500MG
NDA 20427	ORIG 1	OVATION PHARMACEUTICALS INC	SABRIL (VIGABATRIN) TABLET 500MG
NDA 20427	ORIG 1	OVATION PHARMACEUTICALS INC	SABRIL (VIGABATRIN) TABLET 500MG
NDA 20427	ORIG 1	OVATION PHARMACEUTICALS INC	SABRIL (VIGABATRIN) TABLET 500MG
NDA 20427	ORIG 1	OVATION PHARMACEUTICALS INC	SABRIL (VIGABATRIN) TABLET 500MG
NDA 20427	ORIG 1	OVATION PHARMACEUTICALS INC	SABRIL (VIGABATRIN) TABLET 500MG

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

/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

CONTENTS

1	INTRODUCTION AND BACKGROUND.....	3
2	MATERIAL REVIEWED.....	3
3	RESULTS OF REVIEW of Proposed REMS.....	3
3.1	Goals.....	3
3.2	REMS Elements.....	4
3.2.1	Medication Guide.....	4
3.2.2	Communication Plan.....	4
3.2.3	Elements To Assure Safe Use.....	4
3.2.5	Timetable for Submission of Assessments.....	7
3.3	Proposed REMS Assessment Plan.....	7
4	DISCUSSION/RECOMMENDATIONS.....	10
4.1	Recommendations for DNP.....	10
4.2	Recommendations for the Sponsor.....	13
	APPENDICES.....	14

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 with 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.

2.2.4 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;
 - 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.

4.2 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 refractory complex partial seizures and infantile spasms patients who respond/do not respond to Sabril during the treatment initiation phase.

D. Implementation System

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.

APPENDIX II-

**RISK EVALUATION & MITIGATION STRATEGY
SUPPORTING DOCUMENT**

Comment [w1]: Note to the Sponsor:
Attach Appendices 4, 5, & 6 from the
submitted REMS document submitted
July 7 to the REMS Supporting
Document; also attach all Appendices
attached to REMS Supporting Document
submitted July 7.

Title:	Risk Evaluation & Mitigation Strategy (REMS) Supporting Document
Product Name:	Sabril (vigabatrin)
Sponsor:	Lundbeck Inc. Four Parkway North Deerfield, Illinois 60015
Date:	02 July 2009

Confidentiality Statement

The information contained herein is confidential and the proprietary property of Lundbeck Inc. and any unauthorized use or disclosure of such information without the prior written authorization of Lundbeck Inc. is expressly prohibited

TABLE OF CONTENTS

EXECUTIVE SUMMARY	21
1 Background	24
1.1 Identified Risks	24
1.1.1 Vision Loss	24
1.1.2 MRI Abnormality	24
1.2 Identification of Risk and History of Response to Risk by Regulatory Authorities	25
1.2.1 Visual Field Defect	25
1.2.2 MRI Abnormality	26
1.2.3 Suicidality	27
1.3 Populations / Subpopulations at Risk	27
1.3.1 Vision Loss	27
1.3.2 MRI Abnormality	28
1.4 Evaluation of Detection	28
1.4.1 Vision Loss	28
1.4.2 MRI Abnormality	29
1.5 Anticipated Use	30
1.6 Benefit-Risk Assessment	30
1.6.1 Benefit-Risk Assessment in Refractory CPS	30
1.6.2 Benefit-Risk Assessment for Infantile Spasms	31
2 Goals	32
3 SUPPORTING INFORMATION ON PROPOSED REMS ELEMENTS	33
3.1 Medication Guide	33
3.2 Communication Plan	33
3.3 Elements to Assure Safe Use (ETASU)	35
3.4 Roles and Responsibilities for REMS Support	41
3.5 Implementation System	41
3.6 Information Needed for REMS Assessments and Metrics to Evaluate REMS Performance	44
3.6.1 Non-Compliant Prescribing Physicians and Non-Compliant Patients	50
3.7 Monitoring and Evaluation of REMS Third Party Vendors by Lundbeck Inc.	55
3.8 Timetable for Assessment of REMS	56
3.9 Special Safety Surveillance	56
Appendix 1	REMS Process Flow Charts

EXECUTIVE SUMMARY

Sabril (vigabatrin) is an irreversible inhibitor of gamma aminobutyric acid (GABA)-transaminase used for the treatment of certain severe epilepsies including infantile spasms (IS) and refractory complex partial seizures (CPS) in adults. The drug has a well-documented safety profile with the most serious risk being vision loss. Sabril has also been shown to induce an increase in T2 MRI abnormalities in infants with IS.

Sabril causes irreversible bilateral concentric constriction of the visual field 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 and can result in disability. In some cases, Sabril also can damage the central retina and may decrease visual acuity.

The onset of vision loss from Sabril is unpredictable, and can occur within weeks of starting treatment or sooner, or at any time during treatment, even after months or years, although the risk of vision loss may increase with increasing duration of exposure. There is no dose known to be free of risk of vision loss, although the risk of vision loss may increase with increasing dose and cumulative exposure. The possibility that vision loss can worsen despite discontinuation of Sabril has not been excluded.

The effectiveness of Sabril in achieving improved seizure control should be evident within approximately 12 weeks of initiating therapy in adults and 2-4 weeks in infants. In patients with no clinically meaningful seizure improvement, Sabril should be discontinued. For patients with clinically meaningful seizure improvement, clinicians and patients/parent or legal guardian need to have continuing discussions of benefit-risk.

In a retrospective, epidemiological clinical study in pediatric patients with IS Sabril was associated with an increase in the occurrence of T2 signal changes in certain brain regions using magnetic resonance imaging (MRI). The study produced evidence to support a Sabril dose effect since patients receiving a higher dose of Sabril (≥ 125 mg/kg/d) were at greater risk of developing an abnormal MRI. The MRI abnormalities were generally transient, whether or not Sabril was continued. To date, no long-term clinical consequence of these imaging abnormalities has been identified.

Because of the development of vision loss, a comprehensive Risk Evaluation and Mitigation Strategy (REMS) will accompany the commercialization of Sabril in the United States (US). In addition, due to T2 MRI abnormalities in infants with IS, a Phase IV prospective longitudinal study in infants with IS will be conducted to better characterize this finding.

There are relatively few patients with epilepsy who will be appropriate for Sabril treatment and therefore the appropriate benefit-risk assessment for patient selection is critical. There is a concentrated group of approximately 3500 specialists (epileptologists and pediatric neurologists) who treat patients with refractory epilepsy or IS. The REMS tools and resources will target this physician group and their patients.

Proposed indications for Sabril include use as monotherapy of IS and for adjunctive treatment of refractory CPS in adults, two devastating conditions that affect relatively few

people, but if uncontrolled carry extremely poor prognoses. Infantile spasms is associated with significant morbidity and mortality. Most subjects if untreated will have significant, in some cases severe, cognitive impairment. In addition to the severity of the disease state, there are significant risks associated with the unapproved treatment Adrenocorticotropic Hormone (ACTH) currently used for IS in the US. The risks of ACTH include serious infection, cardiomyopathy, and death.

Refractory seizures in adults are associated with significant morbidity and mortality from accidental injury, burns, drowning, suicide, and sudden death. Sudden unexplained death in epilepsy (SUDEP) accounts for 7-17% of deaths among people with epilepsy, and patients with uncontrolled seizures are at the greatest risk of SUDEP.

Given the potential for significant morbidity and mortality associated with uncontrolled seizures in these groups, the population of patients with IS and refractory CPS, the potential of Sabril therapy to improve control of their seizures outweighs the risk of developing vision loss.

The proposed REMS takes into account the consequences of uncontrolled seizures as well as the potential risks and benefits of Sabril. This REMS is based on the 2007 FDA Amendments Act, Title IX, Subtitle A, Sec 505-1 "RISK EVALUATION AND MITIGATION STRATEGIES" and the 2005 FDA Guidance on the Development and Use of Risk Minimization Action Plans. It was developed with input and guidance from key stakeholders that included key opinion leaders, specialty physicians, advocacy groups and patients. The primary goals of this REMS are:

1. To reduce the risk of 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.
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.

In order to achieve these goals, the following objectives must be met:

- Prescribing physicians will be knowledgeable regarding approved clinical indications, the risk of Sabril induced vision loss, and vision monitoring requirements.

- Ophthalmic professionals monitoring patients treated with Sabril will be knowledgeable about the risk of Sabril induced vision loss and vision monitoring requirements.
- Prescribing physicians will be knowledgeable regarding the findings of treatment emergent T2 MRI changes in infants with IS on Sabril therapy.
- Prescribing physicians will understand the how to assess individual patient's benefits and risks of continuing Sabril therapy.
- Patients/parent or legal guardian will be knowledgeable regarding approved clinical indications, the risk of Sabril induced vision loss, and vision monitoring requirements.
- Parent or legal guardian will be knowledgeable regarding the findings of treatment emergent T2 MRI changes in infants with IS on Sabril therapy.
- Patients/parent or legal guardian will be knowledgeable about the risks of suicidal thoughts or behavior.

The REMS-specific activities (tools) with which to reach these objectives were developed with key stakeholders, and are designed to clearly and concisely convey relevant information to key stakeholders (physicians, patients, parent/legal guardian) on the benefits and risks associated with the use of Sabril. The Sabril REMS employs a multifaceted approach using Targeted Education & Outreach and Reminder Systems. The REMS tools will be employed at multiple points along the patient assessment and treatment continuum in an effort to increase awareness and influence the desired stakeholder behavior. The effectiveness of the REMS tools in achieving the established goals and objectives will be evaluated using surveys (physician/ophthalmic professional/patient/parent or legal guardian), specialty pharmacy database, and Lundbeck Inc.'s safety databases. Lundbeck Inc. will provide these assessments to FDA and recommend enhancements and modifications to the REMS based on evaluations of the program's effectiveness.

2 BACKGROUND

3.1 IDENTIFIED RISKS

Vision loss associated with Sabril usage has been identified as a risk. In addition, T2 MRI abnormalities in patients with IS can occur during Sabril therapy.

3.1.1 *Vision Loss*

Sabril causes irreversible bilateral concentric constriction of the visual field 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 and can result in disability. In some cases, Sabril also can damage the central retina and may decrease visual acuity.

The onset of vision loss from Sabril is unpredictable, and can occur within weeks of starting treatment or sooner, or at any time during treatment, even after months or years, although the risk of vision loss may increase with increasing duration of exposure. There is no dose known to be free of risk of vision loss, although the risk of vision loss may increase with increasing dose and cumulative exposure. The possibility that vision loss can worsen despite discontinuation of Sabril has not been excluded.

Miller et al. at Johns Hopkins examined 32 patients while they were taking vigabatrin and reported that 20 of the 32 had visual acuity of 20/20 or better and that the remaining 12 had reduced visual acuity, ranging from 20/25 to 20/60 in one or both eyes.

3.1.2 *MRI Abnormality*

Concern about the possible occurrence of intramyelinic edema (IME) in humans as a result of Sabril therapy for epilepsy is based primarily on 2 observations:

- 1) The occurrence of IME in rodents and dogs treated chronically and subchronically with Sabril.
- 2) Case reports of MRI signal abnormalities in a reproducible anatomical distribution, similar to that of IME in animal models, in infants treated with Sabril for IS.

These data include case reports in the literature and reports by individual physicians captured by postmarketing safety surveillance. These reports are of infants with IS treated with Sabril, typically at a dose above 125 mg/kg/day, who were found to have symmetric regions of diffuse high T2 and FLAIR signal and restricted diffusion in the globus pallidus and thalamus. In some cases the abnormalities extended into brainstem and deep cerebellar nuclei. The imaging abnormalities resolve over weeks to months with discontinuation, maintenance, or a dose reduction of Sabril. Some of the most pressing questions to the practicing clinician include whether there are any clinical signs associated with the imaging abnormalities, and most importantly, whether there are any long-term sequelae. Long-term prospective studies will be required to address these questions. Moreover, with no

histopathological data from infants treated with Sabril who developed MRI signal abnormalities, the MRI findings cannot definitely be equated with IME.

3.2 IDENTIFICATION OF RISK AND HISTORY OF RESPONSE TO RISK BY REGULATORY AUTHORITIES

Sabril was first approved in the UK in 1989 for the treatment of epilepsy and is currently available in more than 50 countries. According to exposure estimates presented in Periodic Safety Update Reports (PSURs), the number of patients exposed to Sabril worldwide is greater than 1.5 million.

3.2.1 Visual Field Defect

Between initial marketing in November 1989 and January 1997, 28 reports of visual field abnormalities were reported worldwide in an estimated 140,000 patients who had received Sabril. After reviewing this safety concern, the Medicines and Healthcare Products Regulatory Agency of the United Kingdom concluded in late 1997 that the association between Sabril and peripheral visual field defect (pVFD), although still requiring further investigation, warranted clear warnings in the Summary of Product Characteristics (SPC). The issue was also referred to the European Medicines Agency (EMA) in early 1998, which instituted a review of this safety issue under an Article 12 proceeding to better understand the site of injury, incidence, prevalence, time course, potential for regression, and to make a decision on continued approval. This led to the initiation of a large multinational cohort study (Aventis Study 4020) to estimate prevalence and incidence of pVFD in pediatric and adult refractory CPS patients treated with Sabril. The EMA ultimately concluded in October 1999 that the benefit-risk balance of Sabril was favorable and that the Marketing Authorizations in the European Union (EU) should be maintained with the following provisions:

- Restriction of the indications to treatment in combination with other anti-epileptic drugs for adult patients with resistant partial epilepsy with or without secondary generalization, that is where all other appropriate drug combinations have proved inadequate or have not been tolerated and to monotherapy in the treatment of IS (West syndrome).
- Initiation of the treatment by a specialist in epileptology, neurology or pediatric neurology and follow-up should be arranged under supervision of a specialist in epileptology, neurology or pediatric neurology.
- Inclusion of warnings in relation to the occurrence of pVFD and the need for systematic screening examination of patients when starting Sabril and at regular intervals for detection of pVFD.
- Update of the section of Undesirable Effects including a wording on pVFD and their severity, onset and prevalence.
- Aventis (the MA Holder in the EU) should fulfill EMA requirements with regard to:

- Preclinical studies: Preclinical studies should be performed to investigate the mechanisms of Sabril induced retinotoxicity and to provide information regarding the possible differences in sensitivity to retinotoxicity in young and adult animals.
- Clinical studies: Clinical studies to evaluate the frequency, severity, progression and reversibility of pVFD should be performed.
- Patient follow-up: Patient follow-up should include data on the prevalence and characteristics of pVFD in children who have been exposed to Sabril and 6 month reviews of follow-up data from marketed use and spontaneous reports should be performed.

Sabril remained on the market in Europe so that, given the risks associated with uncontrolled epilepsy and the benefit-risk profile associated with other antiepileptic drugs, the final decision whether to use Sabril or other antiepileptic drugs would remain an individual benefit-risk judgment in the context of clinical management of an incurable condition.

3.2.2 MRI Abnormality

Dr. Philip Pearl of Children's National Medical Center reported MRI signal changes, consistent with IME, in 3 infants treated with VGB for IS. These findings were presented at a national meeting in October 2006 and have subsequently been published. These new data again raised the question of whether VGB could induce IME in humans and, if so, whether there were clinical accompaniments or sequelae. This concern was reinforced by the reports of 10 additional cases of MRI abnormalities associated with VGB captured through postmarketing safety surveillance and by a report of 6 possible cases in a draft manuscript, since published provided to Lundbeck Inc. by Dr. Olivier Dulac of Necker-Enfants Malades University Hospital, Paris, France.

In response to this issue, Lundbeck Inc. convened an expert review panel composed of senior pediatric epileptologists and neuroradiologists in February 2007. This expert panel advised that a retrospective study in IS patients should be conducted to define incidence and prevalence of such abnormalities.

The retrospective epidemiologic study of IS was designed to determine whether Sabril causes MRI signal changes in this population and, if so, their incidence and prevalence. Given the irregular timing of MRI examinations, the analysis compared the prevalence and incidence during vigabatrin treatment with other treatments for IS and was not based on patient years of exposure.

The results of the study showed that Sabril exposure has a clear and statistically significant association with an increased frequency of the pre-specified MRI abnormalities compared to non-Sabril treated infants with IS. The incidence of such abnormalities was 36% in Sabril exposed subjects, compared to 5.9% in Sabril non-exposed subjects ($p=0.031$). There was evidence for a dose effect, in that subjects exposed to ≥ 125 mg/kg/day Sabril had an incidence of 41.7% of pre-specified MRI abnormalities, whereas subjects exposed to < 125 mg/kg/day had a lower incidence of 33.3%. However, this difference did not achieve

statistical significance, (p=0.099). The prevalence of pre-specified MRI abnormalities in Sabril exposed subjects was 21.5%, compared to 4.1% in the VGB-naïve subjects (p<0.001). This is consistent with prior estimates of the prevalence of VGB-associated MRI abnormalities of 10-20%. Results of this study, as well as the observations of Pearl, and clinicians in France and Finland also indicate that the MRI abnormalities are transient, at least in the majority of cases, and they are more likely to be found in infants exposed to high-doses (≥ 125 mg/kg/d) rather than low-dose VGB.

In the Pearl abstract, the pre-publication paper of Desgeurre, and in the Lundbeck Inc. reviews and study, there is no evidence of any clinical sequelae. In 3 Finnish children, descriptions of abnormal motor movements coincident with the findings of MRI abnormalities led to an EMEA review. In these cases, the abnormal movements resolved following discontinuation of VGB. Therefore, although the data are far from definitive, no evidence of long-term clinical sequelae of the MRI abnormalities has been identified. The EMEA concluded that the benefit-risk balance remained acceptable and no change in the indication for VGB as initial therapy for the treatment of IS was warranted. An amendment to the Undesirable Effects section of the Summary of Product Characteristics was added, stating “Cases of cytotoxic oedema or related abnormal MRI findings/increase in signal intensity have been reported” and “Movement disorders, including dystonia, dyskinesia and hypertonia have in rare cases been seen, either alone or in single cases in association with abnormalities in an NMR”.

3.2.3 Suicidality

FDA has become aware of new safety information indicating an increased risk of suicidal thoughts and behavior with antiepileptic drugs. An increased risk of suicidal thoughts and behavior was demonstrated in an FDA meta-analysis (dated May 23, 2008) of randomized, parallel-arm, placebo-controlled clinical trial data for 11 AEDs. 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); the estimated incidence of suicidal behavior or ideation was 0.43% among 27, 863 drug-treated patients and 0.24% among 16, 029 placebo-treated patients. This finding was generally consistent among drugs in the data analyzed. It was shared by drugs with varying mechanisms of action and was observed for all indications studies; this observation suggests that the risk applies to all AEDs regardless of indication of use.

This new analysis was considered “new safety information” as defined in FDAAA and as such, the FDA requires that all AEDs labeling contain suicidal behavior and ideation information in the WARNINGS and PRECAUTIONS section and Information for Patients section. In addition, all AEDs are required to have a REMS program that consists of a Medication Guide.

3.3 POPULATIONS / SUBPOPULATIONS AT RISK

3.3.1 Vision Loss

The risk for developing vision loss may increase with total dose and duration of use. Alternatively, it might be that people with a genetic variation have a much higher risk than

the general population, who have a low but non-zero risk. Interactions among risk factors, as well as the possibility of factors not yet discovered, are areas for further investigation.

Both IS and refractory CPS, if not adequately treated, yield a high rate of morbidity and mortality. However, in those patients for whom their disease is not adequately controlled with other antiepileptic drugs (AEDs), the risk of the vision loss will outweigh the benefit of this drug. Sabril should currently be used only in combination with other AEDs for patients with refractory complex partial epilepsy when several alternative treatments have proved inadequate or have not been tolerated. Patients or parent/legal guardian must have a clear understanding of the risk of vision loss, and of the recommended vision monitoring that is required for early detection.

3.3.2 MRI Abnormality

There is a causal relationship of Sabril treatment for IS and the occurrence of MRI signal changes in a characteristic anatomical distribution, with symmetric involvement of globus pallidus, thalamus, brainstem and deep cerebellar nuclei.

As noted in the preceding paragraph, IS if not adequately treated, yield a high rate of morbidity and mortality. However, in those patients for whom their disease is adequately controlled with Sabril treatment, the increased risk of MRI signal changes is outweighed by the benefit of this drug. Importantly, no long-term clinical sequelae associated with the imaging abnormalities have been described.

3.4 EVALUATION OF DETECTION

3.4.1 Vision Loss

Sabril causes irreversible bilateral concentric constriction of the visual field 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 and can result in disability. In some cases, Sabril also can damage the central retina and may decrease visual acuity.

The onset of vision loss from Sabril is unpredictable, and can occur within weeks of starting treatment or sooner, or at any time during treatment, even after months or years, although the risk of vision loss may increase with increasing duration of exposure. There is no dose known to be free of risk of vision loss, although the risk of vision loss may increase with increasing dose and cumulative exposure. The possibility that vision loss can worsen despite discontinuation of Sabril has not been excluded.

Vision monitoring at baseline (no later than 4 weeks after starting Sabril) and at least every 3 months while taking Sabril is required. Vision testing is also required about 3 to 6 months after the discontinuation of Sabril therapy. Once detected, vision loss due to Sabril is not reversible, and it is expected that, even with frequent monitoring, the initial detected defect will be of moderate severity in many patients; in some patients, it will be severe.

Patients may not recognize vision loss from Sabril until the vision loss is severe. Vision loss of milder severity, although often unrecognized by the patient, may still adversely affect function.

Sabril should not be used in patients with, or at high risk of, other types of irreversible vision loss unless the benefits of treatment clearly outweigh the risks. The interaction of other types of irreversible vision damage with vision damage from Sabril has not been well-characterized, but is likely adverse. Sabril should not be used with other drugs associated with serious adverse ophthalmic effects such as retinopathy, glaucoma, or macular degeneration unless the benefits clearly outweigh the risks.

The lowest dose and shortest exposure to Sabril should be used that is consistent with clinical objectives.

Monitoring of vision by an ophthalmic professional (defined as having expertise in visual field interpretation and the ability to perform dilated indirect ophthalmoscopy of the retina) is required.

The appropriate diagnostic approach should be individualized for the patient and clinical situation, but for all patients attempts to monitor periodically must be documented under the SHARE program. Perimetry is recommended, preferably by automated threshold visual field testing. Additional testing may also include electrophysiology (e.g., electroretinography [ERG]), retinal imaging (e.g., optical coherence tomography [OCT]), and/or other methods appropriate for the patient. In those patients in whom vision testing is not possible, treatment may continue according to clinical judgment, with appropriate patient counseling and with documentation in the SHARE program of the inability to test vision. Results from ophthalmic monitoring must be interpreted with caution, as reliability and predictive value are variable. Repeat testing in the first few weeks of treatment is recommended to establish if, and to what degree, reproducible results can be obtained, and to guide selection of appropriate ongoing monitoring for the patient.

Vision loss from Sabril may be unpredictable, and may occur or worsen precipitously between tests. Once detected, vision loss due to Sabril is not reversible. It is expected that even with frequent monitoring, some Sabril patients will develop severe vision loss.

3.4.2 MRI Abnormality

For children and adults treated with Sabril for refractory CPS, routine MRI surveillance is unnecessary, as there is no evidence that Sabril causes MRI changes in this population. MRI examinations should be performed as clinically indicated.

For infants treated with Sabril for IS, MRI examination requires sedation and hence carries risk. Moreover, the clinical sequelae of the Sabril-induced MRI changes are unknown. Therefore, routine MRI surveillance of this population is not recommended. In cases where treatment decisions would be dependent on the MRI findings, an MRI one month after starting treatment and again at 3 months will have a high probability of detecting any Sabril-induced MRI changes based on the known time course of the abnormalities.

If infants with IS develop new findings on neurological examination while taking Sabril, especially motor abnormalities, the clinician may consider an MRI examination taking into account the risk associated with this procedure. If MRI signal changes characteristic of Sabril effects are seen, a decision should be made whether to continue or modify therapy taking into account the benefit of Sabril to the patient.

3.5 ANTICIPATED USE

Based on US population statistics and physician market research, Lundbeck Inc. estimates that at peak year (2018) 11,905 patients (refractory CPS population of 9,643 and IS population of 2,262) will be maintained on Sabril therapy, with the greatest proportion of these in adult refractory CPS. It is anticipated that the primary prescribers of Sabril will be physicians experienced in treating epilepsy. Given that the indications are for complicated diseases, prescribers will be specialists in the field of neurology, pediatric neurology, and epileptology. These physicians will be targeted to receive information about the product, the vision loss and the associated vision monitoring recommendations.

3.6 BENEFIT-RISK ASSESSMENT

3.6.1 *Benefit-Risk Assessment in Refractory CPS*

- Refractory CPS is a serious and life-threatening disease and an unmet medical need exists. Although approximately 64% patients with epilepsy achieve complete seizure control with minimal side effects on monotherapy or polytherapy with 2 drugs, the remaining 36% remain refractory to treatment.
- Uncontrolled epilepsy is associated with considerably higher rates of mortality and SUDEP than controlled seizures.
- The efficacy of Sabril for refractory CPS, as add-on therapy, was established in 2 adequate and well-controlled pivotal studies, in a design that remains the current standard for testing AEDs. Statistically significant and clinically meaningful reductions in seizure frequency were observed. Among responders, onset for these improvements was generally noted within 6 weeks of the initiation of treatment.
- Although Sabril is associated with risks, in particular vision loss, other available treatments are not without risks, and all drugs require careful benefit-risk considerations.
- Sabril causes irreversible bilateral concentric constriction of the visual field 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 and can result in disability. In some cases, Sabril also can damage the central retina and may decrease visual acuity. The onset of vision loss from Sabril is unpredictable, and can occur within weeks of starting treatment or sooner, or at any time during treatment, even after months or years, although the risk of vision loss may increase with increasing duration of exposure. There is no dose known to be free of risk of vision loss, although the risk of vision loss may increase with increasing dose and cumulative exposure. The possibility that vision loss can worsen despite discontinuation of Sabril has not been excluded. Vision loss from Sabril may be unpredictable, and may occur or worsen precipitously between tests. Once detected, vision loss due to Sabril is not reversible.
- The risk for vision loss can be managed through a comprehensive Risk Evaluation and Mitigation Strategy (REMS) that focuses on educating prescribing physicians, ophthalmic professionals, and patients: mandatory registration of prescribing physicians and patients into

the Sabril registry; controlling distribution to facilitate prescribing in accordance with its intended use in appropriate patients where an unmet need exists; providing guidance regarding active assessment and management of patients receiving treatment; mandatory benefit-risk assessment after treatment Evaluation Phase (patients with IS and refractory CPS who do not achieve clinically meaningful seizure control will be removed from Sabril after 2-4 weeks and within 3 months of treatment, respectively); providing a reminder system for patient vision monitoring; and enforcing vision monitoring .

- The potential benefits of Sabril treatment outweigh the risks in adult patients with refractory CPS.

3.6.2 *Benefit-Risk Assessment for Infantile Spasms*

- IS is a catastrophic, rare and refractory type of childhood epilepsy, with an estimated incidence to be between 2 to 5 per 10,000 live births in the U.S.
- Mortality rates are high; up to one-third of infants with IS will die before the age of 3.
- Severe to profound mental retardation is also common in this patient population and approximately half the population suffers from other neurological disorders, such as static encephalopathy (cerebral palsy). Patients with IS also experience severe developmental delay or regression from previously attained milestones.
- There are no currently approved treatments for IS in the U.S. Commonly used off-label therapies such as ACTH and prednisone, while demonstrating initial efficacy in patients, are characterized by a high relapse rate (up to 40% in some studies), bringing efficacy to a much smaller number of patients. Other off-label therapies such as valproic acid, benzodiazepines and some newer AEDs, have been used, but efficacy has not been established in controlled studies, nor are they without risks.
- The efficacy of Sabril in patients with IS is established and supported by 2 prospective controlled studies, 2 uncontrolled studies, and additional uncontrolled clinical studies reported in the literature. Pivotal clinical Study 1A is the largest prospective study ever conducted in patients with IS. Findings from this study are supported by multiple controlled and uncontrolled clinical studies that in aggregate demonstrate that spasm cessation is achieved in 30-80% of Sabril treated patients.
- Onset of Sabril efficacy is within 2-4 weeks and the drug is effective across etiologies of IS. Spasm cessation is maintained in about 80% of responding infants.
- Sabril is the drug of choice for IS for physicians outside the U.S.
- Retinal toxicity is a risk for infants treated with Sabril.. Patients who do not achieve clinically meaningful seizure control after 2-4 weeks of treatment will be removed from Sabril therapy.
- In those infants who respond to Sabril with cessation of spasms and resumption of neurological development, vision monitoring should include visual acuity and visual

field whenever possible. The appropriate diagnostic approach should be individualized for the patient and clinical situation.

- Sabril is associated with the development of MRI abnormalities in infants. These MRI changes have been reported to resolve, whether Sabril is continued or stopped. The only clinical findings reported to date are transient motor abnormalities in several patients; however, longitudinal clinical observations are lacking to establish whether the MRI changes have long-term clinical sequelae.
- The benefits of Sabril exceed the risks in patients with IS.

3 GOALS

The proposed REMS focuses on achieving the following 6 goals:

1. To reduce the risk of 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.
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

In order to achieve these goals the following objectives must be met:

- Prescribing physicians will be knowledgeable regarding approved clinical indications, the risk of Sabril induced vision loss and vision monitoring requirements.
- Ophthalmic professionals monitoring patients treated with Sabril will be knowledgeable about the risk of Sabril induced vision loss and vision monitoring requirements.
- Prescribing physicians will be knowledgeable regarding the findings of treatment emergent T2 MRI changes in infants with IS on Sabril therapy.
- Prescribing physicians will understand how to assess individual patient's benefits and risks of continuing Sabril therapy.
- Patients/parent or legal guardian will be knowledgeable regarding approved clinical indications, the risk of Sabril induced vision loss and vision monitoring requirements.

- Parent or legal guardian will be knowledgeable regarding the findings of treatment emergent T2 MRI changes in infants with IS on Sabril therapy.
- Patients/parent or legal guardian will be knowledgeable about the risks of suicidal thoughts or behavior.

4 SUPPORTING INFORMATION ON PROPOSED REMS ELEMENTS

The proposed Sabril REMS includes the following elements;

- A Medication Guide for patients/parent or legal guardian
- A Communication Plan for ophthalmic professionals with education to reinforce key risk messages
- Elements to Assure Safe Use (ETASU) of Sabril in patients including: mandatory registration of physicians and patients into a restricted distribution program, physician attestation that he/she has experience treating epilepsy, a mandatory benefit-risk assessment prior to the beginning of maintenance treatment, a vision monitoring reminder system, enforced ophthalmologic monitoring, for patients with refractory complex partial seizures (CPS) and infantile spasms ((S), establishment of a patient registry, and education for the patient/parent or legal guardian to reinforce key risk messages.

The REMS program will impact prescribing physicians, ophthalmic professionals, and patients/parent or legal guardian, as it is integral to initiating a Sabril prescription and evaluating the benefit-risk proposition. To facilitate familiarity with the REMS and all of its components, we will brand the REMS and the associated services under the acronym S.H.A.R.E which stands for Support, Help and Resources for Epilepsy. Our intent is that physicians and patients become familiar with the SHARE acronym and logo so that they recognize the importance of materials or communications that are branded. All physicians who prescribe Sabril and all patients who take Sabril will be registered in the SHARE program. This will aid in meeting our objective of educating key stakeholders about the benefits and risks associated with Sabril.

3.1 MEDICATION GUIDE

The objective of this tool is to provide information to the patient/parent or legal guardian about the risks associated with Sabril therapy. The medication guide will be reviewed and discussed multiple times in the prescription process and 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 be by the specialty pharmacies at each refill and will be included at the end of each product insert.

3.2 COMMUNICATION PLAN

The communication plan includes activities for ophthalmic professional education.

Ophthalmic Professional Education

The objectives of these tools are to ensure that ophthalmic professionals clearly understand the risk of vision loss associated with Sabril therapy and are aware of the requirements for vision monitoring.

Several tools will be employed to educate ophthalmic professionals including:

- **Product Labeling - Sabril Package Insert (PI) with Boxed Warning (BW)**
 The objective of this tool is to clearly highlight the risk of the Sabril induced vision loss. A boxed warning will convey the prevalence, onset, severity, and risk factors associated with the Sabril induced vision loss as well as requirements for vision monitoring. Information presented in the boxed warning will also be incorporated into all promotional and other applicable materials with the appropriate level of prominence.

- **Dear Healthcare Professional letter**
 The objective of this tool is to inform appropriate physicians of Sabril availability, reinforce the key safety messages related to vision loss and requirements for vision monitoring, inform physicians of current understanding of the treatment emergent T2 MRI findings in infants with IS, and highlight the appropriate product indication. This correspondence would be distributed at product launch to the appropriate healthcare professional audiences (e.g., pediatric neurologists epileptologists, ophthalmic professionals).

These tools will be distributed on an ongoing basis and updated as necessary to assure ophthalmic professionals are well informed of the Sabril REMS.

Dissemination Process

Table 1 identifies Lundbeck Inc.'s plans to disseminate Communication Plan material to ophthalmic professionals.

Table 1. Dissemination of Sabril Communication Plan Materials

Communication Plan Material	Mechanism, Timing and Audience for Dissemination		
	Direct Mail	SHARE Website	Lundbeck Inc. Field Representatives
<i>Ophthalmic Professional</i>			
Package Insert (PI) with Boxed Warning	At product launch to all registered ophthalmologists ^a	X	Field representatives will call on neuro-ophthalmologists and/or

Table 1. Dissemination of Sabril Communication Plan Materials

Communication Plan Material	Mechanism, Timing and Audience for Dissemination		
	Direct Mail	SHARE Website	Lundbeck Inc. Field Representatives
			ophthalmologists at key epilepsy centers at launch and will have PIs available
Dear Healthcare Professional Letter	At product launch to all registered ophthalmologists ^a		
<p>^a Mailing list will include physicians (Medical Doctors [MDs] and Doctors of Osteopathy [DOs]) who are accredited specialists in Ophthalmology. Lists will be derived from the official association membership files (updated weekly and tracked via their Medical Education numbers). The American Medical Association (AMA) oversees the MDs and the American Osteopathic Association (AOA) handles the DOs. Every physician that graduates from a residency program into one of these specialties is tracked by either the AMA or the AOA. Our most current counts reflect: Ophthalmologists (OPH) as: MDs = 18,246 and DOs = 408. These numbers reflect physicians who call OPH their Primary Specialty.</p>			

3.3 ELEMENTS TO ASSURE SAFE USE (ETASU)

1. Mandatory Registration of Physicians and Patients into a Restricted Distribution Program

Prior to any prescription being filled by one of the specialty pharmacies, the prescribing physician and the patient must be registered in SHARE (Support Help And Resources for Epilepsy). The SHARE Call Center will act as the hub for a network of select specialty pharmacies. Participation in both SHARE and the patient registry is mandatory. The SHARE program will serve to ensure that Sabril is only prescribed by physicians with experience in treating epilepsy and that physicians and patients/parent or legal guardian have been properly educated on Sabril's indications, benefits and risks, and associated vision monitoring requirements.

Only physicians with experience in treating epilepsy and who have registered and attested to receiving and understanding Sabril informational material may prescribe Sabril. Patients will only be registered in SHARE to receive Sabril treatment if they have prescriptions written by physicians who are registered in SHARE.

Several tools will be used to ensure that prescribing physicians with experience in treating epilepsy are properly educated regarding appropriate patient selection for Sabril treatment; clearly understand the risks and benefits associated with Sabril therapy; are aware of available educational tools and resources and are aware of the requirements for vision monitoring.

These tools include:

- Sabril Package Insert (PI) with Boxed Warning (BW)
- Dear Healthcare Professional (HCP) Letter
- Dear HCP Taper Letter (Noncompliance with Vision Monitoring)
- Dear HCP Medication Taper Letter (Noncompliance with Benefit-Risk Assessment at Conclusion of Treatment Evaluation Phase)

These tools will be distributed on an ongoing basis and updated as necessary to assure prescribing physicians are well informed of the Sabril REMS.

At product launch, the Sabril package inserts (with boxed warning) and a Dear Healthcare Professional Letter will be sent via direct mail to all registered neurologists and pediatric neurologists. The mailing list will include physicians (Medical Doctors [MDs] and Doctors of Osteopathy [Dos] who are accredited specialists in neurology or pediatric neurology. Lists will be derived from the official association membership files (updated weekly and tracked via their Medical Education Numbers). The American Medical Association (AMA) oversees the MDs and the American Osteopathy Association (AOA) handles the Dos. Every physician that graduates from a residency program into one of these specialties is tracked by either the AMA or the AOA.

Our most current counts reflect Neurology (N) as: MDs -13,218 and DOs – 622. Child Neurology (CHN) as: MDs – 1,394 and DOs - 35 These numbers reflect physicians who call N or CHN their primary specialty.

Additionally, the Sabril package insert will also accompany all promotional material left with physicians and will be available on the www.lundbeck.SHARE.com website.

2. Mandatory Benefit-Risk Assessment

The treatment evaluation phase with Sabril will last up to 3 months for patients with refractory CPS and 2-4 weeks for patients with IS. Prior to maintenance treatment with Sabril, a mandatory benefit-risk assessment is required to be performed which will be documented on the Treatment Maintenance Form. The benefit-risk assessment will comprise assessment of seizure response to treatment and occurrence of any Sabril side effects including vision loss. Sabril will be discontinued in patients who do not demonstrate a clinically meaningful improvement in seizure control thereby minimizing risk for occurrence of vision loss. Sabril will also be discontinued if prescribers do not perform the mandatory benefit-risk assessment within the prescribed timeframe.

3. Vision Monitoring Reminder System

Vision monitoring is required to detect and monitor Sabril induced vision loss to facilitate ongoing benefit-risk assessments in patients.

The labeling will contain requirements for periodic vision monitoring and the recommended assessment methods.

A reminder system operated by SHARE will facilitate vision monitoring in patients treated with Sabril. Patients/parent/legal guardian will be reminded via telephone contact or mailed letter by SHARE approximately 45 days and again at 14 days in advance of their required assessment due date to schedule a vision monitoring appointment.

Monitoring of vision by an ophthalmic professional (defined as having expertise in visual field interpretation and the ability to perform dilated indirect ophthalmoscopy of the retina), must be performed at baseline (no later than 4 weeks after starting Sabril) and at least every 3 months while on therapy. Vision testing is also required about 3 to 6 months after the discontinuation of SABRIL therapy.

4. Enforced Vision Monitoring

To ensure that required vision monitoring is completed in patients with refractory CPS , Lundbeck Inc. will enforce monitoring for vision loss via SHARE (with exception of enforcement of the baseline assessment). There is also enforced monitoring for patient with IS, recognizing that vision monitoring in this population is difficult, and that the appropriate diagnostic approach should be individualized for the patient and clinical situation. As noted above, a reminder system in SHARE will exist to remind patients/parents/legal guardians by telephone contact or mailed letter to schedule vision monitoring approximately 45 days and again at 14 days in advance of their required assessment due date. When vision monitoring is due, formal documentation must be received by the SHARE Call Center.

The prescribing physician is responsible for the overall care of their patients including referral to a qualified ophthalmic professional or center that conducts appropriate visual testing. For this reason, the Ophthalmologic Assessment Form is intended solely for use by the prescribing physician. Prescribing physicians will be educated of their responsibility to provide patients with a referral to an appropriate ophthalmic professional; obtain the ophthalmology testing results from the ophthalmic professional; complete the Ophthalmologic Assessment Form; and provide SHARE with the completed Ophthalmologic Assessment Form. In the event an ophthalmic professional faxes a completed Ophthalmologic Assessment Form to SHARE, SHARE will forward the form to the prescribing physician requesting the physician to (1) sign the form; and (2) reinforce with the consultant ophthalmic professional the procedures regarding notification of test results to SHARE.

If an Ophthalmologic Assessment Form is not received by SHARE by the due date, the patient/parent or legal guardian and the prescribing physician's office will be informed via telephone contact or mailed letter that required vision monitoring must be completed within 90 days of the testing due date unless the prescribing neurologist exempts a patient from mandatory testing for one of the reasons identified on the Ophthalmologic Assessment Form.

The labeling will contain requirements for periodic vision monitoring and the recommended assessment methods.

A reminder system operated by SHARE will facilitate vision monitoring in patients treated with Sabril. Patients/parent/legal guardian will be reminded via telephone contact or mailed letter by SHARE approximately 45 days and again at 14 days in advance of their required assessment due date to schedule a vision monitoring appointment.

Monitoring of vision by an ophthalmic professional (defined as having expertise in visual field interpretation and the ability to perform dilated indirect ophthalmoscopy of the retina), must be performed at baseline (no later than 4 weeks after starting Sabril) and at least every 3 months while on therapy. Vision testing is also required about 3 to 6 months after the discontinuation of SABRIL therapy.

4. Enforced Vision Monitoring

To ensure that required vision monitoring is completed in patients with refractory CPS, Lundbeck Inc. will enforce monitoring for vision loss via SHARE (with exception of enforcement of the baseline assessment). There is also enforced monitoring for patient with IS, recognizing that vision monitoring in this population is difficult, and that the appropriate diagnostic approach should be individualized for the patient and clinical situation. As noted above, a reminder system in SHARE will exist to remind patients/parents/legal guardians by telephone contact or mailed letter to schedule vision monitoring approximately 45 days and again at 14 days in advance of their required assessment due date. When vision monitoring is due, formal documentation must be received by the SHARE Call Center.

The prescribing physician is responsible for the overall care of their patients including referral to a qualified ophthalmic professional or center that conducts appropriate visual testing. For this reason, the Ophthalmologic Assessment Form is intended solely for use by the prescribing physician. Prescribing physicians will be educated of their responsibility to provide patients with a referral to an appropriate ophthalmic professional; obtain the ophthalmology testing results from the ophthalmic professional; complete the Ophthalmologic Assessment Form; and provide SHARE with the completed Ophthalmologic Assessment Form. In the event an ophthalmic professional faxes a completed Ophthalmologic Assessment Form to SHARE, SHARE will forward the form to the prescribing physician requesting the physician to (1) sign the form; and (2) reinforce with the consultant ophthalmic professional the procedures regarding notification of test results to SHARE.

If an Ophthalmologic Assessment Form is not received by SHARE by the due date, the patient/parent or legal guardian and the prescribing physician's office will be informed via telephone contact or mailed letter that required vision monitoring must be completed within 90 days of the testing due date unless the prescribing neurologist exempts a patient from mandatory testing for one of the reasons identified on the Ophthalmologic Assessment Form.

If an Ophthalmologic Assessment Form is not received by SHARE within 45 days after the testing due date, another reminder will be sent to the patient/parent or legal guardian and the prescribing physician's office by telephone contact mailed letter, advising that unless the completed form is submitted to SHARE, the patient will be removed from Sabril therapy within approximately 45 days (i.e., 90 days after the due date) because of non-compliance with mandatory vision monitoring. If the patient and/or parent/legal guardian indicates that required vision monitoring was performed, but their physician has not submitted formal documentation, the SHARE Call Center will attempt to obtain a completed Ophthalmologic Assessment Form from the prescribing physician.

If an Ophthalmologic Assessment Form is not received by SHARE by 90 days after the testing due date, a Dear Healthcare Professional taper letter will be sent to the prescribing physician indicating that the next months Sabril prescription will not be renewed, and the prescribing physician must fax into SHARE a final prescription to allow for tapering off of Sabril therapy. This letter will provide tapering recommendations from the approved package insert and also emphasize the issues surrounding abrupt withdrawal of Sabril. This will be the final prescription that SHARE will dispense for this patient.

~~While baseline vision monitoring will not be enforced,~~ One of the goals of the Sabril REMS is to ensure that all patients receive a baseline ophthalmologic evaluation (50% of patients within 2 weeks of starting Sabril and 100% within 4 weeks). Lundbeck Inc. via SHARE will employ several procedures and reminders to accomplish this goal.

The Sabril package insert and Prescriber Enrollment and Agreement Form will contain language that the required baseline ophthalmologic evaluation must be completed no later than 4 weeks after starting Sabril therapy. The Treatment Initiation Form will contain in the prescription information, documentation of the name of the ophthalmic professional who will conduct the baseline ophthalmologic evaluation and the date of the scheduled appointment. Additionally, one of the pockets on the Sabril Starter Kit has a place for the prescribing physician to document a referral to a specific ophthalmic professional and the date testing is scheduled for the patient.

A hyperlink will also be made available to patients/parents/legal guardians and prescribing physicians on the www.sabil.net website linking them to "Physician Finder" under which ophthalmic professionals can be located in their area.

If the baseline Ophthalmologic Assessment Form is not submitted by the prescribing physician to SHARE at the same time the Treatment Initiation Form is submitted, both the patient/parent or legal guardian and prescribing physician will be reminded via telephone contact or mailed letter by SHARE 7 days after receipt of the Treatment Initiation Form of the need to conduct a baseline ophthalmologic evaluation.

The Ophthalmologic Assessment Form will be available from the SHARE Call Center and via the www.lundbeckSHARE.com website. The form will document that a patient with refractory CPS was seen by an ophthalmic professional, that the appropriate vision assessment was conducted, and the results of the vision assessment. This form will also be

collected for IS patient for whom appropriate assessments should be individualized for the patient and clinical situation.

5. Establishment of a Patient Registry

Lundbeck Inc. will establish a mandatory patient registry upon Sabril approval. This registry will collect prescriber specialty, patient demographics, diagnosis, prior and concurrent anti-seizure medications, and effectiveness as measured by the proportion of refractory CPS and IS patients responding to Sabril during the treatment initiation phase. Ophthalmologic assessment data that must be collected will contribute to a better understanding of frequency, onset, severity and progression of vision loss.

6. Patient/Parent or Legal Guardian Education

The objective of the Sabril Starter Kit is to provide physicians and healthcare providers with a set of materials to facilitate education and discussion with a patient/parent or legal guardian prior to initiating Sabril therapy. The Sabril Starter Kit will be distributed to physicians and healthcare practitioners by Lundbeck Inc. representatives to facilitate the initiation of Sabril therapy. Components of the kit include:

- **Medication Guide**

The objective of this tool is to provide information to the patient/parent or legal guardian about the risks associated with Sabril therapy. The medication guide will be reviewed and discussed multiple times in the prescription process and will be included in the Sabril Starter Kit and reviewed with the patient by the physician prior to starting the patient on Sabril therapy. The medication guide will also be provided to the patient by the specialty pharmacies at each refill and will be included at the end of each product insert.

- **Patient/Parent or Legal Guardian – Physician Agreement**

The objective of this tool is to provide prescribing physicians with a **Patient/Parent or Legal Guardian - Physician Agreement Form** they can use, as permissible by the physician's institution or practice, with their patients to document the patients' understanding of the risks associated with Sabril therapy. Instead of using the Patient/Parent or Legal Guardian - Physician Agreement provided by Lundbeck Inc., prescribing physicians may use their own similar Patient/Parent or Legal Guardian - Physician Agreement if required by their institution or practice. Due to the unique risk profile of Sabril, this tool has a biphasic sign-off process. The patient/parent or legal guardian and physician should each sign the document after reviewing the Medication Guide and deciding to initiate therapy (Evaluation Phase Agreement). After the evaluation phase (within 3 months for patients with refractory CPS and 2-4 weeks for patients with IS), the patient/parent or legal guardian and physician must discuss the degree of seizure improvement that was observed. If no clinically meaningful improvement was observed, Sabril therapy must be discontinued. However, if clinically meaningful seizure improvement is observed, the patient/parent or legal guardian and physician must discuss the risks and benefits of Sabril maintenance therapy. If the decision is made to proceed with maintenance therapy, the physician must sign the Treatment

Maintenance Form. The signed form must be filed at SHARE so that patient may enter the maintenance treatment.

- **Seizure Diary**

The objective of this tool is to track/assess seizure improvement in patients.

- **Reconstitution and Dosing Instructions for Powder for Oral Solution**

The objective of this tool is to properly instruct parents or legal guardians how to reconstitute and administer doses of Sabril powder for oral solution to their baby.

- **Tools to assist in visual assessments for infants (e.g. toys/finger puppet)**

The objective of these tools is to facilitate confrontation testing in infants.

Table 2 further identifies Lundbeck Inc.'s plans to disseminate educational material to patients/parents/legal guardians.

Table 2. Dissemination of Sabril Patient Educational Materials			
Patient Educational Materials	Mechanism for Dissemination		
	Sabril Patient Starter Kit	SHARE Website	Lundbeck Inc. Sales Representatives (materials provided to physician for subsequent dissemination to patients)
Medication Guide	X	X	
Patient/Parent or Legal Guardian – Physician Agreement	X	X	
Seizure Diary	X	X	X
Reconstitution and Dosing Instructions for Powder for Oral Solution	X	X	X

These tools will be updated as necessary in order to assure patients/parents or legal guardians are well informed of the Sabril REMS.

3.4 ROLES AND RESPONSIBILITIES FOR REMS SUPPORT

Lundbeck Inc. has contracted Theracom to support the Sabril REMS program in its entirety. Theracom will maintain the SHARE Call Center which acts as the REMS coordinating center. Responsibilities of the SHARE Call Center include:

- Provide a toll free number (1-888-45-SHARE) to receive and respond to calls from patients, prescribing physicians, ophthalmic professionals, and pharmacists
- Coordination of communication plan to ophthalmic professionals. Including dissemination of Sabril labeling and Dear HCP Letter.
- Receipt and tracking of all required ETASU forms (Prescriber Enrollment & Agreement Form, Treatment Initiation Form, Treatment Maintenance Form, Ophthalmologic Assessment Form, Starter Kit, and Dear HCP Medication Taper Letter)
- Collection of all Registry data (from ETASU forms) into a central validated database
- Triage treatment forms/prescriptions to specialty pharmacies (SP)
- Provide dispense authorizations with the initial prescription and monthly for refills to the dispensing specialty pharmacies
- Notify Lundbeck Inc. of any reports of adverse events
- Maintain vision monitoring reminder system

The sole responsibility of the specialty pharmacy is to fill prescriptions and send them along with a Medication Guide via direct mail to patients/parent/legal guardian after receiving authorization from the SHARE Call Center.

3.5 IMPLEMENTATION SYSTEM

The implementation system to monitor and evaluate the effectiveness of the REMS will utilize data collected in the SHARE database and Surveys of prescribing physicians, ophthalmic professionals, and patients/parent or legal guardian. REMS elements and data collection tools utilized during prescribing, dispensing and treatment are summarized in the implementation system map below. The detailed process flow chart indicating step-by-step activities during the Sabril treatment process and the reminder system associated with vision monitoring are provided as Appendix 1 in this document.

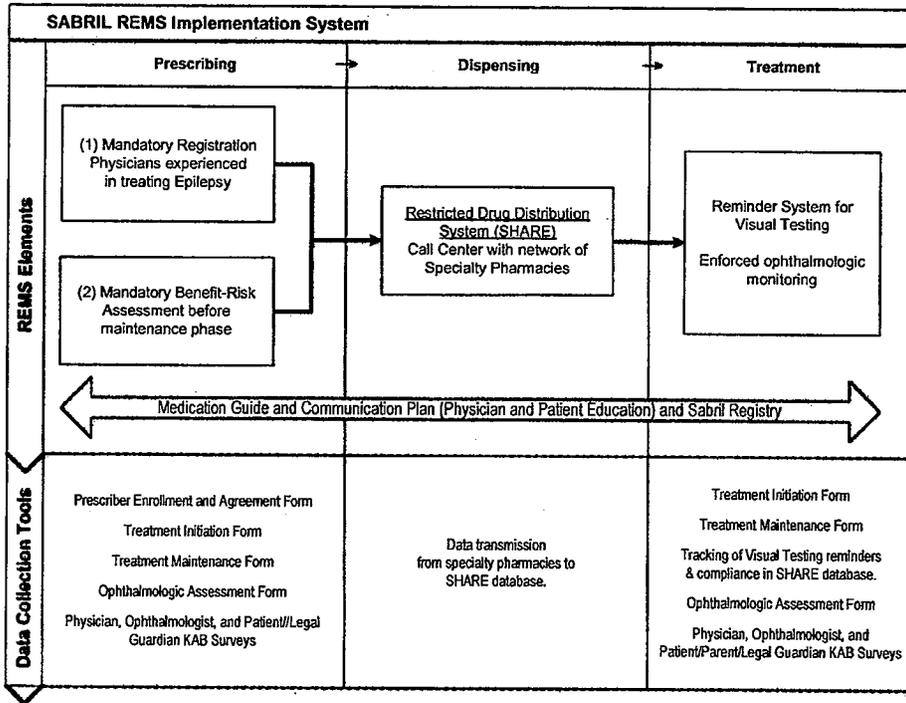
The data collection tools and assessments used to evaluate the restricted distribution and documenting safe use conditions elements of the REMS are described here. The implementation system for other Sabril REMS components are described in the REMS Supporting Document.

Sabril prescriptions can only be dispensed by select specialty pharmacies approved and contracted by Lundbeck Inc. A central call center (SHARE Call Center) will serve a coordinating function and will be administered by a third party vendor, TheraCom. Lundbeck Inc. and TheraCom have generated SOPs that cover all TheraCom responsibilities specific to the requirements for the Sabril REMS program. Specialty pharmacies will be selected according to pre-specified criteria and a formal contractual arrangement requiring adherence to the Sabril REMS requirements is required prior to participation of the specialty pharmacy in the program. Lundbeck Inc. will train and audit both TheraCom and the specialty pharmacies on a regular basis.

A central feature of the Sabril REMS is the documentation of two safe use conditions: performance of a mandatory benefit-risk assessment at the completion of the evaluation phase of treatment and the enforcement of required vision assessments. The Treatment Maintenance Form must be received for all registered patients prior to dispensing Sabril for the maintenance phase of therapy.

Similarly, the Ophthalmologic Assessment Form must be received for all registered patients at required 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.



Detailed step-by-step activities during Sabril treatment process are provided in the process flow charts in Appendix 1.

3.6 INFORMATION NEEDED FOR REMS ASSESSMENTS AND METRICS TO EVALUATE REMS PERFORMANCE

Data will be collected to assess each individual element of REMS.

Medication Guide

Assessment of compliance with distribution of the Medication Guide to patients will involve data collected on a variety of forms to be implemented during the prescription and dispensing stages of treatment and data transmitted directly from the specialty pharmacies to the SHARE database. Completed forms will be stored at the SHARE Call Center. All collected data will be entered in the SHARE Database which will serve as data source for analysis.

Medication Guide	Data Collection Tools for Assessment of Effectiveness	Data Metrics
Provision to Patients/Parent or Legal Guardian.	<ul style="list-style-type: none"> ▪ Treatment Initiation Form ▪ Data transmission from specialty pharmacies to SHARE database. <ul style="list-style-type: none"> • KAB survey for patients with refractory CPS • KAB survey for parents/legal guardians of patients with IS 	<p>Medication Guides</p> <ul style="list-style-type: none"> • # of Medication Guides dispensed • Physician acknowledgment and signature on treatment initiation form that medication guide was reviewed <p>KAB Surveys</p> <ul style="list-style-type: none"> • Level of understanding of SABRIL risks as measured by the score on the KAB survey • # and % of respondents in patient/parent/legal guardian KAB survey who report reading the Medication Guide • # and % of respondents in the patient/parent/legal guardian KAB survey who report they receive a Medication Guide

Medication Guide	Data Collection Tools for Assessment of Effectiveness	Data Metrics
		with each prescription

Communication Plan

Assessment of physician and ophthalmic professional knowledge and understanding of key Sabril safety messages as well as compliance with recommendations for patient management will utilize data collected from Knowledge, Attitude and Behavior (KAB) Surveys. The surveys will be implemented by Lundbeck Inc. according to protocol and using standardized questionnaires distributed to a representative sample of physicians and ophthalmic professionals registered in the SHARE program. Completed questionnaires will be stored with Lundbeck Inc. which will undertake analysis and evaluation of survey results.

Communication Plan	Data Collection Tools for Assessment of Effectiveness	Data Metrics
Physician Education <ul style="list-style-type: none"> • Package Insert with BW • Dear HCP letter • Dear HCP Medication Taper Letter 	<ul style="list-style-type: none"> • Physician KAB Surveys 	<ul style="list-style-type: none"> • The number of physicians in the sample, in total, and by key characteristics • The number of physicians attempted to contact at each wave • Of those attempted to contact: <ul style="list-style-type: none"> ○ # who opt out/ask to be removed from list ○ # who agree to participate in the survey ○ Of those who agree to participate, # who qualify ○ Of those who qualify, # who complete any portion of the interview ○ Of those who qualify, # who complete the survey • Description of survey participants <ul style="list-style-type: none"> ○ Medical specialty - adult or pediatric practice ○ Experience with

Communication Plan	Data Collection Tools for Assessment of Effectiveness	Data Metrics
		<p>SABRIL</p> <ul style="list-style-type: none"> o Geographic region • Frequency distribution of responses to each question ▪ Percent of those answering each response to each question ▪ Percent of respondents indicating correct response to each objective ▪ Additional analyses, included subset by adult or pediatric practice, may be performed if needed
<p>Ophthalmic professional Education</p> <ul style="list-style-type: none"> • Package Insert with BW • Dear HCP Letter 	<ul style="list-style-type: none"> ▪ Ophthalmic professional KAB Surveys 	<ul style="list-style-type: none"> • The number of ophthalmic professionals in the sample, in total, and by key characteristics • The number of ophthalmic professionals attempted to contact at each wave • Of those attempted to contact: <ul style="list-style-type: none"> o # who opt out/ask to be removed from list o # who agree to participate in the survey o Of those who agree to participate, # who qualify o Of those who qualify, # who complete any portion of the interview o Of those who qualify, # who complete the survey • Description of survey participants <ul style="list-style-type: none"> o Experience with

Communication Plan	Data Collection Tools for Assessment of Effectiveness	Data Metrics
		SABRIL <ul style="list-style-type: none"> ○ Geographic region ● Frequency distribution of responses to each question ● Percent of those answering each response to each question ● Percent of respondents indicating correct response to each objective

Elements to Assure Safe Use (ETASU)

Assessment of compliance with ETASU will involve data collected on a variety of forms to be implemented during the prescription and drug use stages of treatment. Completed forms will be stored at the SHARE Call Center. All collected data will be entered in the SHARE Database which will serve as data source for analysis. Assessment of patient/parent/legal guardian knowledge and understanding of key Sabril safety messages will utilize data collected from Knowledge, Attitude and Behavior (KAB) Surveys. The surveys will be implemented by Lundbeck Inc. according to protocol and using standardized questionnaires distributed to a representative sample of patients/parents/legal guardians registered in the SHARE program. Completed questionnaires will be stored with Lundbeck Inc. which will undertake analysis and evaluation of survey results.

Elements To Assure Safe Use	Data Collection Tools for Assessment of Effectiveness	Data Metrics
Mandatory registration of Physicians and Patients <ul style="list-style-type: none"> ● Registration of physicians with experience in treating epilepsy ● Attestation of Physicians 	<ul style="list-style-type: none"> ● Prescriber Enrollment and Agreement Form 	<ul style="list-style-type: none"> ● Comparison of distribution records with list of registered prescribers ● The number and specialties of prescribers registered for the reporting period and cumulatively
Mandatory benefit-risk assessment prior to entering maintenance treatment	<ul style="list-style-type: none"> ○ Treatment Maintenance Form 	<ul style="list-style-type: none"> ○ Comparison of forms received with list of registered patients
Reminder system for Vision Monitoring	<ul style="list-style-type: none"> ○ Tracking in SHARE Database of all reminder contacts made with individual patients. 	<ul style="list-style-type: none"> ● Frequency distribution of number of reminder calls made per patient ● Review of pattern of reminder calls to confirm no gap in therapy
Enforced Vision Monitoring	<ul style="list-style-type: none"> ○ Ophthalmologic 	<ul style="list-style-type: none"> ○ Comparison of ophthalmologic forms with list of registered

Elements To Assure Safe Use	Data Collection Tools for Assessment of Effectiveness	Data Metrics
	Assessment Form ○ Tracking in SHARE database	patients <ul style="list-style-type: none"> ● The number of patients who miss vision monitoring appointments, the reason they miss them, and how long the monitoring is delayed ● The number and % of patients who do not obtain baseline vision monitoring with the first 4 weeks after treatment initiation, by reason, age, and prescriber. ● The number of patients who are at least 60 days late in obtaining required vision monitoring appointments on 3 separate occasions. ○ The number of patients by age who do not complete the required vision monitoring within the REMS evaluation period ○ The number of patients who are exempted from vision monitoring by reason checked on the Ophthalmologic Assessment Form and by prescriber.
Patient Registry	<ul style="list-style-type: none"> ○ Prescriber Enrollment and Agreement Form ○ Treatment Initiation Form ○ Treatment Maintenance Form ○ Ophthalmologic Assessment Form 	<ul style="list-style-type: none"> ○ Comparison of form receipt with list of registered patients ○ The number of patients registered for the reporting period and cumulatively, including the age and gender of the patients
Patient Education <ul style="list-style-type: none"> ● Medication Guide ● Patient/Parent or Legal Guardian-Physician Agreement ● Seizure Diary ● Reconstitution and Dosing Instructions 	<ul style="list-style-type: none"> ○ Patient/Parent or Legal Guardian KAB Surveys 	<ul style="list-style-type: none"> ● Number of patients, parents, and legal guardians who call to volunteer for survey participation ● Number of patients who meet inclusion criteria ● Description of survey participants <ul style="list-style-type: none"> - Indication for SABRIL use - Duration of use (as indicated in SHARE database) - Gender - Age - Geographic region - Status (patient, parent, legal guardian) - Where treated

Elements To Assure Safe Use	Data Collection Tools for Assessment of Effectiveness	Data Metrics
		<ul style="list-style-type: none"> • Frequency distribution of responses to each question (that is, the number of respondents who give each answer to each question) • Percent of those answering each response to each question (in total and separately for patients and caregivers) • Percent of respondents indicating correct response to each objective (in total and separately for patients and caregivers) • Analyses will be stratified by indication for SABRIL use as well as analyses for the combined sample.

Miscellaneous

To further assess REMS effectiveness, the following data will also be collected.

- a. a. The number of Sabril shipments to patients without prior authorization from Lundbeck Inc.
- b. The number of specialty pharmacies who are de-enrolled, with reasons for de-enrollment.

Data Collection Tools for Assessment	Data Assessment/Metric
<ul style="list-style-type: none"> • Ophthalmologic Assessment Form • KAB Surveys 	<ul style="list-style-type: none"> • Narrative summary and analysis of information collected on Ophthalmologic Assessment Forms • Narrative summary and assessments of reports of vision loss • KAB Survey results • The number of patients who discontinue Sabril therapy before the beginning of the maintenance phase. • The number of patients whose therapy is interrupted due to changing

Data Collection Tools for Assessment	Data Assessment/Metric
	prescribers. <ul style="list-style-type: none">• The number of prescribers who are de-registered and reasons.• The number of prescribers who are re-registered and reasons.• The number of patients who are de-registered and reasons.

3.6.1 *Non-Compliant Prescribing Physicians and Non-Compliant Patients*

Non-compliance with the Sabril REMS requirements will be handled in the following manner as described below in Table 3.

Table 3. Criteria and Process for Noncompliance		
Category of Noncompliance	Description	Source/Method of Determination of Noncompliance
Physician Enrollment/Attestation <i>(Prescribing physician)</i>	All prescribers of Sabril must be registered in SHARE and attest to having experience in treating epilepsy and having an understanding of educational materials provided by Lundbeck Inc.	Prescriber Enrollment and Agreement Form
Patient Education <i>(Prescribing physician)</i>	All prescribers of Sabril must certify that they have reviewed the Medication Guide with the patient and/or parent/legal guardian, and have counseled him/her on the risks of SABRIL, including vision loss.	Treatment Initiation Form
Mandatory Benefit/Risk Assessment <i>(Prescribing physician)</i>	Physicians prescribing Sabril for patients with refractory CPS must document a clinically meaningful improvement in seizure control within 3 months of initiating Sabril therapy, and physicians prescribing Sabril for patients with IS must document a clinically meaningful improvement in spasm control within 2-4 weeks of initiating Sabril therapy.	Treatment Maintenance Form
		Criteria/Processes
		<p>A completed Prescriber Enrollment and Agreement Form, signed by the physician, is required for the physician to prescribe Sabril. If the Prescriber Enrollment and Agreement Form is incorrectly filled out, the SHARE Call Center will contact the physician by phone to ensure that the form is completed correctly.</p> <p>A completed and signed Treatment Initiation Form is required for the patient to receive his or her first Sabril prescription. If the Treatment Initiation Form is incorrectly filled out, the SHARE Call Center will contact the physician by phone to ensure that the form is completed correctly.</p> <p>If a Treatment Maintenance Form (documenting the Sabril benefit/risk assessment) is not received for a specific patient, the SHARE Call Center will contact the prescribing physician within 3 working days of when the Treatment Maintenance Form was due to determine whether he or she wishes the patient to continue Sabril therapy. If the physician wishes to continue with Sabril therapy, the SHARE Call Center will facilitate completion of the Treatment Maintenance Form by the physician. If the physician fails to complete and submit the Treatment Maintenance Form within 7 working days after being notified by SHARE, the patient will be titrated off Sabril.</p> <p>If this occurs three times, the physician's attestation will be revoked, his or her prescribing rights will be terminated, and the physician's patients will be provided names and contact information for other prescribing physicians in the area who have registered in SHARE.</p>

Table 3. Criteria and Process for Noncompliance			
Category of Noncompliance	Description	Source/Method of Determination of Noncompliance	Criteria/Processes
Mandatory Benefit/Risk Assessment <i>(Prescribing physician)</i> (continued)			The physician may be re-instated in SHARE at a later date, providing that they undergo training on the Sabril REMS requirements, and certify in writing their commitment and ability to comply with program requirements.
Vision Monitoring <i>(Prescribing physician or patient)</i>	Patients are required to have vision monitoring at baseline (no later than 4 weeks after starting Sabril) and at least every 3 months thereafter while taking Sabril. Vision monitoring is also required about 3 to 6 months after the discontinuation of SABRIL therapy.	Ophthalmologic Assessment Form	To ensure that required vision monitoring is completed in patients, Lundbeck Inc. will enforce monitoring for vision loss via SHARE with exception of the baseline assessment. When vision monitoring is due, formal documentation (Ophthalmologic Assessment Form) must be received by the SHARE Call Center for all patients. If an Ophthalmologic Assessment Form is submitted to SHARE but is incorrectly filled out, the SHARE Call Center will contact the physician by phone to ensure that the form is completed correctly.

Table 3. Criteria and Process for Noncompliance

Category of Noncompliance	Description	Source/Method of Determination of Noncompliance	Criteria/Processes
Vision Monitoring <i>(Prescribing physician or patient)</i> <i>(continued)</i>			<p>A reminder system in SHARE will facilitate vision monitoring in patients treated with Sabril. Approximately 45 days and again at 14 days in advance of the due date of required vision monitoring, patients/parent or legal guardian will be reminded by SHARE via telephone contact or mailed letter to schedule a vision monitoring appointment.</p> <p>If an Ophthalmologic Assessment Form is not received by SHARE by the due date, the patient/parent or legal guardian and the prescribing physician's office will be informed via telephone contact or mailed letter that required vision monitoring must be completed within 90 days of the due date (unless the prescribing neurologist exempts a patient from mandatory testing for one of the reasons identified on the Ophthalmologic Assessment Form).</p> <p>If an Ophthalmologic Assessment Form is not received by SHARE within 45 days after the due date, another reminder will be sent to the patient/parent or legal guardian and the prescribing physician's office by telephone contact or by mailed letter, advising that unless the completed form is submitted to SHARE, the patient will be removed from Sabril therapy within approximately 45 days because of non-compliance with mandatory vision monitoring. If the patient /parent or legal guardian indicates that required vision monitoring was performed, but their physician has not submitted formal documentation, the SHARE Call Center will attempt to obtain a completed Ophthalmologic Assessment Form from the prescribing physician.</p> <p>If an Ophthalmologic Assessment Form is not received by SHARE by</p>

Table 3. Criteria and Process for Noncompliance

Category of Noncompliance	Description	Source/Method of Determination of Noncompliance	Criteria/Processes
			<p>90 days after the due date, the Sabril prescription will not be renewed, and a Dear Healthcare Professional taper letter will be sent to the prescribing physician indicating that a final prescription must be written to allow for tapering off of Sabril therapy. This letter will provide tapering recommendations from the approved package insert and also emphasize the issues surrounding abrupt withdrawal of Sabril. This will be the final prescription that SHARE will dispense for this patient.</p> <p>Noncompliance of the patient will not affect the prescribing physician's status in the SHARE program. However, if prescribing physician non-compliance results in inappropriate discontinuation of Sabril 3 or more times, the physician's attestation will be revoked, his or her prescribing rights will be terminated, and the physician's patients will be provided names and contact information for other prescribing physicians in the area who have registered in SHARE. The physician may be re-instated in SHARE at a later date, providing that they undergo training on the Sabril REMS requirements, and certify in writing their commitment and ability to comply with program requirements.</p>

3.7 MONITORING AND EVALUATION OF REMS THIRD PARTY VENDORS BY LUNDBECK INC.

Lundbeck Inc. and TheraCom have created an internal business requirements document that specifies the administrative requirements for the Sabril REMS program. Lundbeck Inc. intends to host a training program with all TheraCom employees directly responsible for the Sabril REMS program and site managers at the specialty pharmacies. The training will cover the diseases states Sabril is used in, an overview of Sabril, and the business requirements document.

Sabril REMS specific SOPs have been created by Lundbeck Inc. and TheraCom that cover all SHARE Call Center and specialty pharmacies responsibilities listed above in Section 3.4 Roles and Responsibilities for REMS Support. All involved TheraCom and specialty pharmacies employees will be trained on these SOPs.

The only task the specialty pharmacies are held accountable for is the dispensing of Sabril product and Medication Guide via mail to the patients home after authorization has been granted by the SHARE system.

Collection of all registry data (from ETASU forms) is stored in a proprietary database maintained by the SHARE Call Center at TheraCom which associates each record to the proper patient, dispense, doctor, etc as needed to fill needs of each program. Each patient record has a unique key, which is matched at import, to ensure that incoming records are associated with the correct record existing in the system. Database access is controlled via application level security as determined by TheraCom. Data files/records are routinely reviewed by TheraCom and run through system verifications. Each record is then checked to ensure that required fields are present for each record. Should a record be missing a required field the record will be rejected and prompt a response for resolution.

TheraCom has developed a process for identifying and resolving quality issues. Quality issues may include quality of service concerns, divergence from standard operating procedures, or other concerns that represent quality improvement opportunities. When a potential quality issue is identified, the individual who identifies the issue completes a Quality Issue Report and forwards the report to their regional manager, the regional manager then sends the report to SHARE Call Center program manager, a copy of the report is sent to Lundbeck Inc. If the quality issue is identified internally by SHARE Call Center, the issue is reported directly to TheraCom program management.

The Program Manager is then responsible for:

1. Logging receipt of the quality case or issue
2. Indicating the severity of the issue
3. Notification of the TheraCom senior manager and the Lundbeck Inc. point of contact for the support center and other key contacts as required.
4. Conducting and documenting the investigation and follow up on the reported issues with appropriate team members and reporters within two business days.
5. Proposing and implementing corrective action plans where appropriate.

6. Providing cumulative quality reports provided to management and Lundbeck Pharmaceuticals.
7. Tracking the incidence of quality reports for trends and root cause analysis.

The SHARE Call Center holds weekly implementation conference calls with the SP. Discussed are: weekly SP dispense records, reconciliation of the daily and weekly data feeds provided by the SP to the SHARE Call Center, and review of patient status for those patients in the system awaiting Sabril.

A daily patient status report for all patients registered in SHARE is provided by the SHARE Call Center to Lundbeck Inc.

3.8 TIMETABLE FOR ASSESSMENT OF REMS

Periodic assessments of the REMS effectiveness will be performed by Lundbeck Inc. and results will be submitted and discussed with the agency. Assessment of the REMS will involve data collected in the SHARE database and information obtained through conduct of prescribing physicians, ophthalmic professionals, and patient/parent or legal guardian KAB Surveys. It is proposed that these assessments be performed at 6 months, 1 year, and annually thereafter post- approval for a period of 7 years unless FDA requests a longer assessment period.

In addition to formal assessments of the REMS, comprehensive periodic assessments of Pharmacovigilance information (spontaneous and literature reports) for health outcomes will be submitted post approval on a quarterly basis for the first 3 years and annually thereafter. Annual reports of data from the Sabril Registry will also be submitted to FDA.

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.

3.9 SPECIAL SAFETY SURVEILLANCE

Lundbeck Inc. will closely follow up on spontaneous reports of liver injury and attempt to obtain additional follow-up information including a complete description of the case, outcome information, lab test results, biopsy results, and post mortem test results.

All serious liver injury cases will be reported to the Agency as 15-Day reports.

Appendix 1 REMS Process Flow Charts

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

/s/

Mary Dempsey
7/17/2009 08:56:11 AM
DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski
7/17/2009 12:32:21 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.

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

/s/

Mary Dempsey
7/14/2008 07:56:10 AM
DRUG SAFETY OFFICE REVIEWER

Gerald DalPan
7/29/2008 10:35:36 AM
MEDICAL OFFICER



**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 (vigabitrin) Tablets: an Approvable action in November 1997 and a Not Approvable action in October 1998.

2 MATERIAL REVIEWED

- SABRIL (vigabitrin) 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 (vigabitrin) 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 (vigabitrin) Tablets and SABRIL (vigabitrin) for Oral Solution Medication Guide (MG) provided by the review division on May 8, 2009 based on the individual SABRIL (vigabitrin) Tablets MG submitted by the applicant on March 1, 2009 and revised throughout the review cycle, and the proposed SABRIL (vigabitrin) for Oral Solution MG submitted by the applicant on March 8, 2007, and revised throughout the review cycle.

3 DISCUSSION

The applicant submitted an evaluation entitled "Readability Evaluation of SABRIL Medication Guides" as part of their REMS amendment dated March 10, 2009. However, based upon initial review of the proposed individual MGs and discussions with DNP, DRISK recommended to DNP one combined MG for SABRIL (vigabitrin) Tablets and SABRIL (vigabitrin) for Oral Solution. Medication Guides are not for a specific formulation, rather they are for the product. DNP drafted a combined MG for SABRIL (vigabitrin) Tablets and SABRIL (vigabitrin) for Oral Solution and provided this to DRISK on May 8, 2009. Our review is based on DNP's proposed combined MG. For this reason, the applicant's readability study is not relevant. The applicant also submitted an evaluation entitled "Safety and Readability Evaluation of SABRIL Powder Mixing and Administration Instructions" which was reviewed by DMEPA.

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

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 APFont to make medical information more accessible for patients with low vision. We have reformatted the MG document using the font APFont, 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

b(4)

- Under “Risk of suicidal thoughts or actions” we note DDMAC’s comment that the language “very small number of people” is promotional in tone and the recommendation to delete this qualifier. We agree with DDMAC. We also deleted “Like other antiepileptics” to be consistent with DRISK’s recommendation in MGs for other antiepileptic drugs.
 - We moved the bullet that addresses the issue that suicidal thoughts and actions can be caused by other things than medicines, so that it precedes the instruction not to stop taking SABRIL without first talking to a doctor. While this is not consistent with what has been proposed by DRISK in recent reviews of other antiepileptic MGs, it seems more logical to have this information follow the information that SABRIL may cause suicidal thoughts and behaviors, and the reportable symptoms. The review division should clarify whether the information about not stopping SABRIL, as originally placed, is related to suicidal thoughts and behaviors, or is a separate thought.
 - Regarding the bullet “Stopping SABRIL suddenly can cause serious problems”: Patients and caregivers should be informed of what serious problems can occur if they suddenly stop SABRIL. Section 9.3 of the PI says that SABRIL should be gradually withdrawn to minimize increased seizure frequency; however, this part of the MG seems to only speak to suicidal thoughts and actions.
4. In the section “What is SABRIL?” we revised the bullet pertaining to SABRIL for Oral Solution to be consistent with the indication statement in the SABRIL for Oral Solution PI.
 5. We deleted the section “Who should not take SABRIL?” as there are no labeled contraindications to use of the product.
 6. In the section “How should SABRIL be taken?”
 - Under: *If you are an adult with Complex Partial Seizures:*
 - The 5th bullet states: “**Do not stop taking SABRIL suddenly.** This can cause serious problems.” The applicant should explain the “serious problems” that can occur if SABRIL is stopped suddenly. As currently stated in the proposed MG, the information is not useful to patients.
 - We recommend adding the following instruction and a similar instruction to section 17 if the PI: “Tell your doctor right away about any increase in seizures while you are stopping SABRIL.”
 - We deleted the instruction telling patients to ask their doctor before they start taking SABRIL what to do if they miss a dose. A specific instruction should be provided to patients in the MG in the event they miss a dose of SABRIL, particularly since abruptly stopping SABRIL can cause serious problems. If the patient is directed to ask the doctor beforehand about what to do if they miss a dose, they may forget what to do. Since patients will receive the MG, they can refer back to this information.
 - In the bullet “Do not stop taking SABRIL without talking to your doctor” DNP should clarify whether “improve” means less severe, fewer seizures, or both.
 - Under “If you are giving SABRIL to your baby:

- We moved the mixing instructions to the end of the document and named it “Instructions for mixing and giving SABRIL for oral solution to your baby.”
 - The Applicant should add an instruction for what to do if the baby spits out the medicine, vomits, or only takes a partial dose.
 - As in our comment above for adults, information should be added to explain what serious problems can happen if a baby stops receiving SABRIL suddenly.
 - We recommend adding the following instruction and a similar instruction to section 17 of the PI: “Tell your doctor right away about any increase in your baby’s seizures while stopping SABRIL.”
 - We deleted the instruction telling patients to ask their doctor before they start giving SABRIL to their baby what to do if they miss giving the baby a dose. A specific instruction should be provided to patients in the MG in the event they miss giving their baby a dose of SABRIL, particularly since abruptly stopping SABRIL can cause serious problems. If the caregiver is directed to ask the doctor beforehand about what to do if they miss giving their baby a dose, they may forget what to do. Since caregivers will receive the MG, they can refer back to this information.
7. In the section “What are the possible side effects of SABRIL?”
- The review division should clarify whether “position sense” is a clinical assessment or if there is a patient-friendly definition that can be used here for patients to report, such as telling what position part of your body is in.
 - Under “The most common side effects of SABRIL in adults include”:
 - We deleted the bullet for Somnolence and fatigue. Somnolence and fatigue are in the Warnings and Precautions section of the MG; therefore, we address these symptoms as sleepiness and tiredness at the beginning of this section as serious side effects. They do not need to be repeated here.
 - We deleted the bullet for feeling irritable or depressed. Irritability and depression are addressed as symptoms under Risk of Suicidal thoughts and actions in the section “What is the most important information I should know about SABRIL. The reader is referenced back to that section at the top of this section “What are the possible side effects of SABRIL?” since patients are told to report new or worse irritability and new or worse depression, this bullet is unnecessary.
 - Headache is not listed in the Highlights section of the PI; however, it is listed first in PI section 6.1 under Adverse Reactions in US and Primary Non-US Clinical Studies as occurring in 18% of patients. “Headache” is not listed in Table 2. The review division should clarify if headache should be added to Highlights and if it should be moved up to the top of the list of common side effects in the MG.
 - The review division should clarify if the nystagmus seen with SABRIL causes loss of vision or is seen in association with the vision loss that can happen. This bullet may need to be re-worded.

- We added nasopharyngitis (inflamed nose and throat) and diarrhea as these are included in the Highlights section of the PI with the other common side effects listed above.
 - We deleted the bullet for weight gain. Weight gain is in the Warnings and Precautions section of the PI (5.10) and therefore has been added to the list of serious side effects above.
 - The Applicant should clarify it “prickling or itching” refers to symptoms of peripheral neuropathy. Information about peripheral neuropathy is included with the serious side effects as numbness and tingling, because it is in the Warnings and Precautions section of the PI (5.9). If this is the case, delete this bullet.
 - The bullet for “disorientation” was deleted. The review division should clarify the inclusion of “disorientation” as a common side effect. Memory problems are already addressed above. In table 2, “confused state” occurred in 6% of SABRIL patients.
 - The bullet for numbness and tingling was deleted. Numbness and tingling is already included under serious side effects under the bullet for peripheral neuropathy.
8. In the section “What are the ingredients in SABRIL?” we revised the list of inactive ingredients in SABRIL Tablets to be consistent with section 11 of the PI.

We have the following comments on the “Instructions for mixing and giving SABRIL for oral solution to your baby”:

9. The instructions provided by the applicant in the MG closely follow the brochure “Instructions for preparing and giving your baby SABRIL” submitted by the applicant in their REMS amendment dated March 10, 2009. However, unlike the brochure, the instructions in the MG are not accompanied by any figures. The applicant should add labeled figures adjacent to the corresponding text for each step below, beginning with the needed supplies. The figures should be referenced in the text. Figures that show the syringes should have increased prominence so that the markings are clearly shown. Avoid using circles to highlight markings; instead use an arrow pointing to the marking so that the view is not obscured. In the figure entitled “syringe detail” the applicant should label all parts of the syringe. For example, the applicant refers to the “bottom ring” of the plunger in step 8. The applicant should clarify whether oral syringes are provided. If so, the figures should reflect oral syringes.
10. The Dosage and Administration section of the IS PI states that the product should be prepared immediately before use and administered cold or at room temperature. The review division should clarify for the purposes of the caregiver what is meant by “room temperature.” For storage, we give a temperature range.
11. The applicant should clarify if oral syringes will be provided for dosing.
12. In step 13:
- The PI does not clarify how long it takes for the powder to dissolve. For this reason, we have not added the statement “This may take several minutes” because this language is not currently in the draft PI. The MG must be consistent with the PI.
 - The review division should clarify what the caregiver should do if the solution does not become clear.

13. The instruction for washing the syringes and mixing cups does not seem adequate. The applicant should provide more specific and detailed cleaning instructions for the syringes and mixing cups.
14. We defer to DMEPA regarding any recommendation that the applicant should repeat their evaluation for use of the instructions for mixing and giving SABRIL (vigabatrin) for Oral Solution.

Please let us know if you have any questions.

37 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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

/s/

Sharon Mills
6/5/2009 12:56:09 PM
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: 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	3
	1.1 Introduction	3
	1.2 Regulatory History	3
	1.3 Product Information.....	4
2	METHODS AND MATERIALS.....	4
3	RESULTS AND DISCUSSION	5
	3.1 Sabril for Oral Solution	6
	3.2 Medication Guide Statement for Labels and Labeling for Sabril Tablets and Sabril for Oral Solution.....	6
4	RECOMMENDATIONS	6
	4.1 Comments to the Applicant	6
5	REFERENCES	8
	5.1 Review of Safety Applications	8
6	APPENDICES	9

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 _____), providing educational tools which include _____ a 'Dosing Instruction Sheet for Patients/Caregivers' and revising language on their proposed foil packets.

b(4)

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)

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

December 23, 2008 - Sabril for Oral Solution (NDA #22-006)

- Container Labels-Samples A and B
- Dosing Instruction Sheet for Patients/Caregiver

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

DMRPA 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 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, _____, to help them evaluate and revise their instructions for use. _____ 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.

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

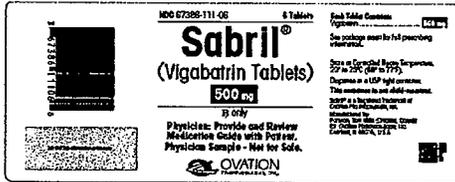
5.1 REVIEW OF SAFETY APPLICATIONS

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

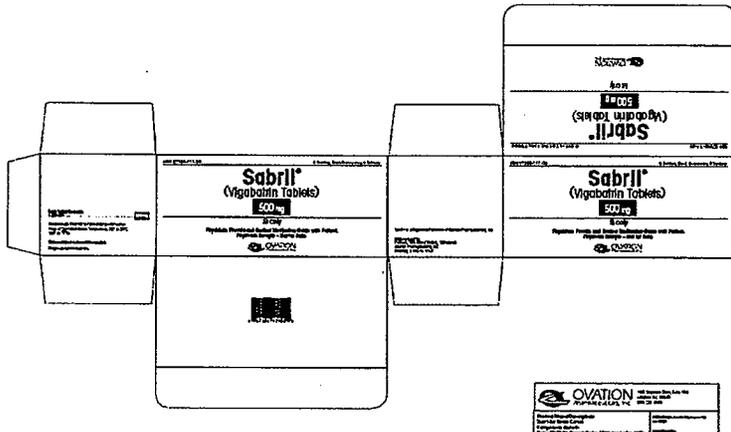
Appendix A: Sample Container Label for Sabril Tablets – 6 count (Note: Images not to scale)



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 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 _____ 10 mL and 3 mL Oral Syringes)

b(4)

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)

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

/s/

Tselaine Jones-Smith
5/6/2009 12:42:48 PM
DRUG SAFETY OFFICE REVIEWER

Kristina Arnwine
5/6/2009 01:36:38 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
5/6/2009 04:16:45 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

**Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
HFD-420; White Oak BLDG 22, Room 4447
Center for Drug Evaluation and Research**

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

Through: Nora Roselle, Pharm.D., Team Leader
Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, HFD-420

From: Judy Park, Pharm.D., Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Date: November 9, 2006

Subject: DMETS Proprietary Name, Label, and Labeling Review
NDA#: 20-427 Sabril (Vigabatrin) Tablets, 500 mg
NDA#: 22-006 Sabril (Vigabatrin) for Oral Solution, 500 mg

Project #s: 2006-603 & 2006-757

This memorandum was written in response to a request from the Division of Neurology Products (HFD-120), for a re-assessment of the proprietary name, Sabril and a review of the revised labels and labeling. DMETS comments on the Risk Minimization Action Plan (RiskMAP) for Sabril will be included in the OSE RiskMAP review. DMETS first evaluated the name, Sabril, for the indication of use of Refractory Complex Partial Seizures in OSE Consults #'s 05-0250 and 05-0250-1, dated July 6, 2006, and found the proposed proprietary name acceptable at that time.

I. NAME REVIEW

Since our original review, the Sponsor has submitted an additional NDA for Sabril which includes a new dosage form and indication of use (oral solution for Infantile Spasms). Because of this revision, DMETS re-reviewed the names from our previous consult to determine if the new dosage form, dosing, and indication of use pose any new safety concerns that were not considered at the time of initial review. Following consideration of the new product characteristics, we have concluded that the new dosage form, dosing and indication of use do not pose any concerns with the names previously reviewed.

However, DMETS has identified one additional proprietary name, Teril, with potential for confusion with Sabril which was not captured in the previous review. Teril is a proprietary name for the generic drug carbamazepine. Both names end with the same three letters (-ril). However, the beginning letters of each name (Te- vs. Sab-), the additional letter in Sabril (five letters vs. six letters), as well as the upstroke letter of "b" in Sabril noticeably differentiate the names when scripted (see sample on page 2).

Teril
Sabril

Both products have an overlapping indication of use (seizures), route of administration (oral), frequency of administration (twice daily), and dosage form (oral tablet and oral solution/suspension). Both drugs are dosed in mg/kg/day then converted to an mL equivalent for the total dose. Sabril and Teril are both available in a single product strength (200 mg tablets vs. 500 mg tablets, 100 mg/5 ml oral suspension vs. 500 mg oral solution) which therefore does not need to be indicated on a prescription order. Additionally, Teril is available in a bottle of liquid oral suspension and Sabril is available as powder which requires reconstitution prior to oral administration. Since Teril is a brand name of a generic product, it may be more likely that a prescription will be ordered by the brand name (e.g. Tegretol) or the established name (e.g. carbamazepine). In addition, while the name is listed in Drugs@FDA, Orange Book, NDC Directory, and Micromedex, Teril is not found in Facts & Comparison, Clinical Pharmacology, The 2006 Redbook, or DSS. Similarly, the name Teril was identified in Saegis as being available in several foreign countries, but is not listed in the United States. Thus, despite the overlapping product characteristics, DMETS believes the orthographic differences and the limited use of the name will help to decrease the risk of confusion and error between Teril and Sabril.

II. LABEL AND LABELING REVIEW

The Sponsor has submitted revised labels and labeling in response to DMETS comments dated July 10, 2006. We note that the Sponsor has addressed most of the concerns noted in our original review. However, DMETS has the following additional recommendations for revisions to minimize medication errors.

A. GENERAL COMMENTS

1. "Sachet" is not a recognized proper dosage form listed in the USP. DMETS consulted Guirag Poochikian, Acting Chair of the CDER Labeling and Nomenclature Committee for the proper designation of the established name and dosage form. He advised that the proper designation of the established name should be "(Vigabatrin) for Oral Solution." If you have further questions regarding the proper established name and dosage form, please contact Guirag Poochikian for further discussion. In addition, "sachet" is not an easily recognizable packaging unit. Please replace all references of "sachet" with the proper dosage form or recognizable packaging unit (e.g. packet) in all the labels and labeling.

B. CONTAINER LABELS (Tablets and Sachets)

1. If space permits, per 21 CFR 201.55, please include a usual dose statement (e.g. Usual dosage: See package insert for full prescribing information).
2. As per 21 CFR 208.24, the authorized dispenser is to "provide" a Medication Guide to each patient and a statement of how the Medication Guide will be provided must be included. Please

change the reminder statement for the pharmacists, _____
reflect this regulation. In addition, the regulation states that “these statements shall appear on the label in a prominent and conspicuous manner.” We recommend increasing the font size of this statement as it is not prominent and maybe easily overlooked.

C. CARTON LABELING (Tablets and Sachets)

1. See comments B1-B3.
2. For the tablet carton labeling, please revise the net quantity statement to read _____

D. INSERT LABELING

1. Highlights of Prescribing Information – *Indications and Usage*
 - a. Please include “in Adults” after the first bullet “Refractory Complex Partial Seizures” to be consistent with the full prescribing information.
 - b. Please define the age range for the indication of infantile spasms so that the prescriber has a clear understanding of the patient’s age limit.
2. Full Prescribing Information
 - a. Section 1 - *Indications and Usage*
 - i. Under Section 1.2, please insert the age range for the indication of infantile spasms so that the prescriber has a clear understanding of the patient’s age limit.
 - b. Section 2 - *Dosage and Administration*
 - i. Under Section 2.1, the dosage and administration instructions for Refractory Complex Partial Seizures in Adults are to give the doses in “two divided doses.” Please clarify if the two divided doses should be 12 hours apart or some other specified time frame.
 - ii. Under Section 2.2, the dosage and administration instructions for Infantile Spasms are confusing. The first sentence “Sabril 500 mg sachets should be given as twice daily oral administration with or without food” implies that 500 mg should be given twice daily (e.g. 1000 mg/day). But the later instructions indicate that infants should be dosed based on weight (mg/kg/day). Because of these dosing instructions, it is conceivable that doses lower than 500 mg will be required. Thus, there should be clear instructions on how to administer only the required amount of drug in volume measurement. A final solution concentration should also be included (500 mg/10 mL = 50 mg/mL). DMETS is concerned that there will be cases of underdosing or overdosing with incorrect calculation of the doses especially with a complex titration schedule as listed.

b(4)

- iii. Under Section 2.2, please include instructions on what to do with the leftover solution (e.g. discard unused portion, use immediately after mixing) as noted on the labels and labeling.
 - iv. For Section 2.2, please be consistent in the instructions in other labeling (e.g. Medication Guide, carton labeling). In the Medication Guide (question #4) and carton labeling, instruction is given to “dissolve” the drug in liquid but in the full prescribing information, instruction is given to “mix.”
 - v. Under Section 2.3, *Patients with Renal Impairment*, patients with renal impairments are categorized by their creatinine clearance. However, the recommended dose adjustment is based on patient’s creatinine concentration and not clearance. Please be consistent. Revise accordingly.
 - vi. Under Section 2.4, *General Dosing Considerations*, it is recommended when discontinuing Sabril, “the dose should be gradually reduced.” However, there are no instructions on how to “gradually reduce” the dose (e.g. reduce in increments of 500 mg per day?). Revise accordingly.
- c. Section 8 - *Use in Specific Populations*
- i. Under Section 8.3 *Pediatric Use*, please define the age range for the indication of infantile spasms.

In summary, DMETS has no objections to the use of the proprietary name, Sabril. DMETS also recommends implementation of the label and labeling recommendations outlined above. Additionally, DDMAC finds the proprietary name acceptable from a promotional perspective.

We consider this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward. If you have any questions or need clarification, please contact Diane Smith, Project Manager, at 301-796-0538.

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

/s/

Judy Park
12/18/2006 09:52:57 AM
DRUG SAFETY OFFICE REVIEWER

Nora L. Roselle
12/18/2006 10:06:45 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
12/18/2006 10:54:58 AM
DRUG SAFETY OFFICE REVIEWER