DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20427/S-014
NDA 22006/S-015

**SUPPLEMENT APPROVAL**

Lundbeck LLC
Attention: Gregg Pratt, PhD
Acting Vice President, Regulatory Affairs
Four Parkway North
Deerfield, IL 60015

Dear Dr. Pratt:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received February 24, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Sabril (vigabatrin) tablets and oral solution.

We also acknowledge receipt of your amendments dated January 9, 2016, February 3, 2016, March 22, 2016, March 28, 2016, April 15, 2016, June 15, 2016, and June 16, 2016.
These Prior Approval supplemental new drug applications provide for proposed modifications to the approved Sabril (vigabatrin) risk evaluation and mitigation strategy (REMS) and corresponding changes to the Sabril (vigabatrin) Prescribing Information and Medication Guide. The supplements, as amended, were submitted in response to our October 6, 2015, REMS Modification Notification letter.

## APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at

http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

## REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

## RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Sabril (vigabatrin) was originally approved on August 21, 2009, and the most recent modification was approved on October 26, 2013. The REMS consists of a Medication Guide, a communication plan, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS. In order to minimize burden on the healthcare delivery system of complying with the REMS and because certain elements of the REMS are no longer necessary to ensure that the benefits of Sabril outweigh its risks, we determined that you were required to make the following REMS modifications:

1. Modified goals
2. Removal of the Medication Guide and communication plan as elements of the REMS
3. Removal of ETASU that require:
   - each patient using the drug be enrolled in a registry
4. Modifications to ETASU that require:
   - healthcare providers who prescribe the drug have particular training or experience, or are specially certified

- pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
- the drug be dispensed to patients with evidence or other documentation of safe-use conditions

5. Modifications to the implementation system
6. Modifications to the timetable of submission of assessments

Your proposed modified REMS, submitted on June 15, 2016, and appended to this letter, is approved. The modified REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS must be revised to be submitted one year from the date of the approval of the REMS modification, and annually thereafter.

The revised REMS assessment plan must include, but is not limited to, the following:

For each annual SABRIL REMS Program assessment report, provide the following information. For each category, provide the information for the current reporting period and for each previous reporting period. A tabular format is acceptable when appropriate.

A. Program outreach

1. Letters *(insert name of the letter here)*: date(s) sent, numbers sent, route (email, U.S. mail)

2. For letters sent by email: proportion opened

3. For letters sent to societies, provide the actions taken by the societies (e.g., letter posted to website, distributed to members, no action)

4. Number, name, and date of scientific meetings in which SABRIL REMS Program materials were displayed

B. Program utilization

1. Certification of healthcare providers (HCP)

   a. Number of new certifications of HCP; indicate whether previously certified or not

   b. Number of active HCP (have prescribed Sabril at least once during the reporting period) in outpatient pharmacy settings

2. Certification of pharmacies

    a. Number of new certified inpatient or outpatient pharmacies

    b. Number of active certified outpatient pharmacies (have filled or ordered at least one prescription for Sabril during the reporting period)

        a. For certified inpatient pharmacies provide the number of orders shipped during the assessment period

3. Patient enrollment

    a. Number of new patients enrolled

    b. Number of active patients (have received at least one shipment of Sabril during the reporting period) in outpatient pharmacy settings

C. SABRIL REMS Program Call center

1. Number of contacts by stakeholder type (patient/caregiver, prescriber, pharmacy, other)

2. Summary of frequently asked questions (FAQ) by stakeholder type

D. Program performance/compliance

1. Audits: Summary of audit findings for audits conducted during the reporting period by type, including any corrective and preventive actions (CAPA)

2. Number of prescribers and pharmacies de-certified and reasons for decertification

3. Number of Sabril prescriptions dispensed that were written by non-certified prescribers and any action taken and outcome of action (e.g., provision of educational program materials, prescriber became certified)

4. Number of prescriptions dispensed by non-certified pharmacies and the actions taken to prevent future occurrences.

5. Number of shipments sent to non-certified pharmacies, sources of report, and actions taken to prevent future occurrences

6. Summary of any additional non-compliance, source of report, resulting corrective and preventive actions (CAPA)

E. Evaluation of knowledge through Knowledge, Attitude and Behavior (KAB) surveys

1. Prescribers

a. An evaluation of knowledge of certified prescribers of the increased risk of vision loss, the need to counsel patients and caregivers about the risk, and the need for periodic visual monitoring.
b. An evaluation of prescriber practice or behavior with regards to counseling patients and caregivers about the increased risk of vision loss and the need for periodic visual monitoring and documentation of counseling.

2. Patients

a. An evaluation of knowledge of patients or caregivers of the increased risk of vision loss, and the need for periodic visual monitoring.
b. An evaluation of patients' or caregivers' recall of counseling by prescriber on the risk of vision loss and the need for periodic visual monitoring.

F. Overall SABRIL REMS Program evaluation

As required for assessments of an approved REMS under section 505-1(g)(3), the Applicant will include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.
e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**NDA ###### REMS CORRESPONDENCE**
**(insert concise description of content in bold capital letters, e.g.,**
**UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

**NDA ###### REMS ASSESSMENT**

**NEW SUPPLEMENT FOR NDA ######/S-000**
**CHANGES BEING EFFECTED IN 30 DAYS**
**PROPOSED MINOR REMS MODIFICATION**

***or***

**NEW SUPPLEMENT FOR NDA ######/S-000**
**PRIOR APPROVAL SUPPLEMENT**
**PROPOSED MAJOR REMS MODIFICATION**

***or***

**NEW SUPPLEMENT FOR NDA ######/S-000**
**PRIOR APPROVAL SUPPLEMENT**
**PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX**

***or***

**NEW SUPPLEMENT (NEW INDICATION FOR USE)**
**FOR NDA ######/S-000/ SECONDARY TRACKING NUMBER**
**REMS ASSESSMENT**
**PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

**REMS REVISIONS FOR NDA ######**

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

**REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact E. Andrew Papanastasiou, Regulatory Project Manager, via email at emilios.papanastasiou@fda.hhs.gov or phone at (301) 796-1930.

Sincerely,

*{See appended electronic signature page}*

Alice Hughes, MD
Deputy Director for Safety
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
REMS

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

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/s/

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ALICE HUGHES
06/21/2016