NDA 20427/S-019
NDA 22006/S-021

SUPPLEMENT APPROVAL

Lundbeck Pharmaceuticals LLC
Attention: Michael Bigda
Senior Manager, US Regulatory Strategy
Six Parkway North, Suite 400
Deerfield, IL 60015

Dear Mr. Bigda:

Please refer to your supplemental new drug applications (sNDAs) dated December 4, 2018, received December 4, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Sabril (vigabatrin) tablets and powder for oral solution.

These Prior Approval supplemental new drug applications provide for proposed modifications to the approved Vigabatrin risk evaluation and mitigation strategy (REMS). We acknowledge that your application included a rationale to support the proposed REMS modifications.

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 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 (REMS) REQUIREMENTS

The REMS for Sabril was originally approved on August 21, 2009, and the Single Shared System (SSS) REMS for vigabatrin products was originally approved on April 27, 2017. The most recent REMS modification for the SSS was approved on October 23, 2017. The Vigabatrin REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modifications to the REMS consist of changes to allow for the continuation of therapy for patients currently enrolled in the Vigabatrin REMS by an uncertified prescriber in the inpatient setting, and incorporating the requirement that a certified prescriber must authorize additional vigabatrin dispenses for these patients within 15 days of inpatient admission. The REMS document and Pharmacy Enrollment Form were revised to align with these changes. The REMS document was also revised to align with the *Format and Content of a REMS Document Guidance for Industry.*

Your proposed modified REMS, submitted on December 4, 2018, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on April 27, 2017.

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

A. Program utilization (per reporting period and cumulatively)

1. Certification of healthcare providers (HCP)
   a. Number of new certifications of HCP; indicating whether previously certified or not.
   b. Number of active HCP (have prescribed vigabatrin at least once during the reporting period) in outpatient pharmacy settings.

2. Certification of pharmacies
   a. Number of new certified inpatient and outpatient pharmacies.
   b. Number of active certified outpatient pharmacies (have filled or ordered at least one prescription for vigabatrin during the reporting period).
   c. For certified inpatient pharmacies, the number of orders shipped during the assessment period.

3. Patient enrollment
   a. Number of new patients enrolled, stratified by age groups
   b. Number of active patients (have received at least one shipment of vigabatrin during the reporting period) in outpatient pharmacy settings stratified by age groups

4. Drug utilization
   a. Number of prescriptions by patient age for each reporting period and cumulatively
   b. Number of prescriptions by pharmacy type for each reporting period and cumulatively

B. Vigabatrin REMS Program Contact center (per reporting period and cumulatively)

1. Number of contacts by stakeholder type (patient/parent/legal guardian, prescriber, pharmacy, other).
2. Summary of frequently asked questions (FAQ) by stakeholder type.

C. Program performance/compliance (per reporting period and cumulatively)

1. Audits: Summary of audit findings for audits conducted during the reporting period by pharmacy type, including any corrective and preventive actions (CAPA).
2. Number of prescribers and pharmacies de-certified and reasons for decertification.
3. Number of vigabatrin prescriptions dispensed that were written by non-certified prescribers or for non-enrolled patients, a root-cause analysis of each event, including associated unique pharmacy number, actions taken to prevent future occurrences (e.g., provision of educational program materials, prescriber became certified), and a monitoring plan to determine the success of actions taken.
4. Number of inpatient pharmacies that continued to dispense beyond 15 days of inpatient admission without verifying a certified prescriber authorizes continuing vigabatrin for an enrolled patient
5. Number of prescriptions dispensed by non-certified pharmacies, a root-cause analysis of each event, including associated unique pharmacy number; actions taken to prevent future occurrences (e.g., provision of educational program materials, pharmacy staff re-education), and a monitoring plan to determine the success of actions taken.
6. Number of times certified pharmacies either bypassed REMS authorization processes and dispensed vigabatrin OR did not receive authorization from the REMS to dispense the drug but dispensed it anyway.
7. Number of shipments sent to non-certified pharmacies, sources of report, and actions taken to prevent future occurrences.
8. Summary of any additional non-compliance, source of report, resulting corrective and preventive actions (CAPA).

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

1. Prescribers

a. An evaluation of stakeholder knowledge of certified prescribers of the increased risk of vision loss, the need to counsel patients and parents/legal guardians about the risk, and the need for periodic visual monitoring.

b. An evaluation of prescriber practice or behavior with regards to:
   i. counseling patients and parents/legal guardians about the increased risk of vision loss, and the need for periodic visual monitoring.
   ii. documentation of counseling.
   iii. mitigation of potential vision loss (such as referring patients for periodic vision monitoring).

2. Patients
   a. An evaluation of knowledge of patients or parents/legal guardians of the increased risk of vision loss, and the need for periodic visual monitoring.
   b. An evaluation of patients' or parents/legal guardians' recall of counseling by prescriber on the risk of vision loss and the need for periodic visual monitoring as well as patients' recall of the frequency of their vision monitoring.

The requirements for assessments of an approved REMS under section 505-1(g)(3) 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 1 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 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

or

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 LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA ######/S-000
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, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no

later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

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, call LaShawn Dianat, Regulatory Project Manager, at (240) 402-7713.

Sincerely,

{See appended electronic signature page}

Eric Bastings, M.D.
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
- REMS

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIC P BASTINGS
05/31/2019 06:44:30 AM