DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020427/S-010/S-011/S-012
NDA 022006/S-011/S-012/S-013

SUPPLEMENT APPROVAL

Lundbeck LLC
Attention: Mahlaqa Patel
Director, Regulatory Affairs
Four Parkway North, Suite 200
Deerfield, IL 60015

Dear Ms. Patel:

Please refer to your Supplemental New Drug Applications (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

NDA / Supplement Number	Product Name	Submitted on:	Received on:
NDA 020427/S-011/S-012	Sabril (vigabatrin) tablet 500 mg	April 25, 2013	April 26, 2013
NDA 022006/S-012/S-013	Sabril (vigabatrin) powder for oral solution 500 mg	April 25, 2013	April 26, 2013

We acknowledge receipt of your amendments dated:

May 31, 2013	June 10, 2013	June 13, 2013	June 18, 2013
June 19, 2013	July 1, 2013	July 2, 2013	July 3, 2013
July 10, 2013	July 17, 2013	August 7, 2013	August 15, 2013
September 17, 2013	October 1, 2013	October 8, 2013 (2)	October 14, 2013
October 17, 2013			

We also acknowledge your risk evaluation and mitigation strategy (REMS) assessment dated September 9, 2013.

These "Prior Approval" supplements provide for:	
NDA 020427 / S-011 Sabril (vigabatrin) tablet 500 mg	• expanding the use of Sabril tablets as adjunctive therapy in children 10-16 years of age with refractory complex partial seizures • proposed modifications to the approved REMS
NDA 020427 / S-012 Sabril (vigabatrin) tablet 500 mg	• combining the separate, previously approved package insert for Sabril tablet and Sabril powder for oral solution into a single package insert

These "Prior Approval" supplements provide for:	
NDA 022006 / S-012 Sabril (vigabatrin) powder for oral solution 500 mg	• the addition of information regarding duration of therapy for infantile spasms in the Pediatric subsection and the Clinical Studies section of the labeling • proposed modifications to the approved REMS
NDA 022006 / S-013 Sabril (vigabatrin) powder for oral solution 500 mg	• the use of Sabril powder for oral solution as adjunctive therapy in the treatment of refractory complex partial seizures for adults and pediatric patients ≥ 10 years of age • proposed modifications to the approved REMS • combining the separate, previously approved package insert for Sabril tablet and Sabril powder for oral solution into a single package insert

These Prior Approval supplemental new drug applications are submitted as responses to the Pediatric Written Request dated April 18, 2013, for vigabatrin. The above applications propose changes to the labeling based on clinical data necessary to fulfill the requirements of the Pediatric Written Request.

The submissions also contain the final study reports and analyses for the postmarketing requirement under the Pediatric Research Equity Act (PREA PMR 1526-1), and the postmarketing requirement(s)/commitment(s) (PMR/PMC 1523-1, 1523-4, 1523-5) listed in the August 21, 2009 approval letters.

We also refer to your Supplemental New Drug Applications (sNDA) for the following:

NDA / Supplement Number	**Product Name**	**Submitted & Received on:**	**Amended on:**
NDA 020427/S-010	Sabril (vigabatrin) tablet 500 mg	Nov 9, 2012	Dec 21, 2012
NDA 022006/S-011	Sabril (vigabatrin) powder for oral solution 500 mg	Nov 9, 2012	Dec 21, 2012
These "Changes Being Effected" supplements provide for:			
the addition of information regarding Stevens-Johnson syndrome and toxic epidermal necrolysis in the Postmarketing Experience subsection of the labeling.			

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

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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 (text for the package insert, Medication Guide, and Instructions for Use), 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 includes 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.

1. Refractory Complex Partial Seizures

   We reference the partial waiver granted on August 21, 2009, for the pediatric study requirement for Sabril (vigabatrin) tablet, NDA 020427. We waived the pediatric study requirement for ages birth to 10 years because necessary studies are impossible or highly impracticable. Evidence strongly suggests that Sabril (vigabatrin) would be unsafe in this pediatric group. The visual toxicity of Sabril would be difficult to monitor in children 10 years of age and younger and other drugs are available to treat complex partial seizures, even refractory seizures. Thus, any possible benefit of Sabril (vigabatrin) used in this population appears to be clearly outweighed by its risks.

   With this action, we are also partially waiving the pediatric study requirement for Sabril (vigabatrin) powder for oral solution, NDA 022006. This partial waiver is for refractory complex partial seizures in pediatric patients ages birth to 10 years because necessary studies are impossible or highly impracticable.

   We note that you have fulfilled the pediatric study requirement (PMR 1526-1) for the treatment of refractory complex partial seizures in pediatric patients ages 10 to 16 years for these applications.

2. Infantile Spasms

   Because Sabril (vigabatrin) powder for oral solution, NDA 022006, for the treatment of infantile spasms has an orphan drug designation, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENT(S) AND COMMITMENT(S)

Your submission dated April 25, 2013, contained the final report and analyses for the following postmarketing requirements listed in the August 21, 2009, approval letters for NDA 020427 and NDA 022006.

1523-1 A toxicology study in the juvenile rat examining the potential for vigabatrin exposure during development to produce neuronal damage. The study protocol should be submitted to the Division for comment prior to study initiation.

1523-4 An open label clinical trial to assess the single and multiple dose (at steady state) pharmacokinetics of Sabril (vigabatrin) at a clinically relevant dose in infants with infantile spasms who are 1-5 months of age.

1523-5 An adequately controlled trial in infants treated with Sabril (vigabatrin) for infantile spasms to further characterize the minimum duration of therapy required for sustained suppression of spasms. It is possible that a shorter duration of therapy will mitigate the risk of vision damage. The protocol for the trial should be discussed with the Agency prior to being submitted as a special protocol assessment (SPA).

We have reviewed your submission and conclude that the above requirement(s)/commitment(s) were fulfilled.

We remind you that there are postmarketing requirements listed in the August 21, 2009, approval letters for NDA 020427 and NDA 022006 that are still open.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Sabril (vigabatrin) was originally approved on August 21, 2009, and REMS modifications were approved on January 18, 2011, and December 11, 2012. The REMS consists of a Medication Guide, communication plan, elements to assure safe use, implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of revisions to the Medication Guide, the REMS document, the Prescriber Enrollment and Agreement Form, and the Patient/Parent/Legal Guardian-Physician Agreement Form to include information regarding the expanded indication for complex partial seizures to patients $\geq$ 10 years of age.

Your proposed modified REMS, submitted on October 4, 2013, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS will remain the same as that approved on December 11, 2012.

There are no changes to the REMS assessment plan described in our December 11, 2012 letter.

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 one or more such goals or such elements should be modified.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

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 20427 / 22006 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.

Prominently identify the 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 20427 / 22006 REMS ASSESSMENT**
>
> **NEW SUPPLEMENT FOR NDA 20427 / 22006**
> **PROPOSED REMS MODIFICATION**
>
> **NEW SUPPLEMENT (NEW INDICATION FOR USE)**
> **FOR NDA 20427 / 22006**
> **REMS ASSESSMENT**
> **PROPOSED REMS MODIFICATION (if included)**

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

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

> Food and Drug Administration
> Center for Drug Evaluation and Research
> Office of Prescription Drug Promotion (OPDP)
> 5901-B Ammendale Road
> Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html;

instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

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

Because of increases in alkaline phosphatase observed in the controlled pediatric trials, we ask that you include an analysis of elevations in alkaline phosphatase in pediatric patients as a part of your annual reports. This should include a tabulated analysis of incidence in clinical trials, postmarketing data, and publications. Potential causality and significance should be included in a narrative discussion.

If you have any questions, contact Fannie Choy, Regulatory Project Manager, by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):
Content of Labeling
REMS

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

/s/

ERIC P BASTINGS
10/26/2013