DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-427 **NDA APPROVAL**

Lundbeck Inc.
Attention: Jenny Swalec, Sr. Director
Global Regulatory Affairs
4 Parkway North, Suite 200
Deerfield, IL 60015

Dear Ms. Swalec:

Please refer to your new drug application (NDA) dated April 29, 1994, received May 2, 1994, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sabril (vigabatrin) Tablets, 500 mg.

Reference is also made to the Agency's Not Approvable Letter dated April 28, 1995, Approvable Letter dated November 26, 1997, and Not Approvable Letter dated October 27, 1998.

We acknowledge receipt of your additional correspondence and amendments dated:

December 28, 2007	February 11, 2008	February 12, 2008	March 14, 2008
April 10, 2008	April 15, 2008	April 23, 2008	April 25, 2008
May 2, 2008	May 6, 2008	May 7, 2008	May 14, 2008
May 15, 2008	May 16, 2008	May 23, 2008	May 27, 2008
May 29, 2008	June 2, 2008	June 2, 2008	June 4, 2008
June 6, 2008	June 6, 2008	June 11, 2008	June 18, 2008
June 20, 2008	June 26, 2008	June 30, 2008	July 23, 2008
July 25, 2008	August 4, 2008	October 31, 2008	November 21, 2008
November 24, 2008	November 24, 2008	November 26, 2008	December 24, 2008
January 12, 2009	January 30, 2009	February 5, 2009	February 5, 2009
February 12, 2009	February 19, 2009	February 24, 2009	March 10, 2009
March 25, 2009	April 2, 2009	April 9, 2009	April 21, 2009
April 30, 2009	June 22, 2009	July 7, 2009	July 14, 2009
July 29, 2009	August 18, 2009		

The December 28, 2007, submission constituted a complete response to our October 27, 1998, action letter.

This new drug application provides for the use of Sabril (vigabatrin) Tablets for Refractory Complex Partial Seizures in Adults.

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

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.

We are waiving 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.

We are deferring the requirement for pediatric studies for ages 10 to 16 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study, required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act, is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. The required study is listed below:

1526-1: Deferred pediatric study under PREA for the treatment of Refractory Complex Partial Seizures in pediatric patients ages 10 to 16.

The study is to be a multi-center, randomized, placebo-controlled double blind parallel-design study evaluating the safety and efficacy of several fixed doses of Sabril (vigabatrin) as adjunctive therapy in pediatric patients age 10 years and above with refractory complex partial seizures. Adequate visual monitoring and stopping rules must be incorporated into this study.

Protocol Submission Date:	by October 2009
Study Completion Date:	by January 2014
Final Report Submission:	by April 2014

Submit final study reports to this NDA. Use the following designator to prominently label all submissions:

"**Required Pediatric Assessment(s)**".

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to:

- Assess the known serious risk of vision loss with Sabril (vigabatrin) and the potential mechanisms for mitigating the vision loss.
- Identify the unexpected serious risk for Sabril (vigabatrin) to induce CYP1A2 and CYP3A4 enzymes. Induction of these enzymes could result in the loss of effect of antiepileptic and other drugs that are metabolized by these enzymes, and therefore could increase the risk of adverse outcomes including seizures.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

1526-2: A study analyzing data from the Registry provided for in the REMS to evaluate the development of visual lesions, timing and risk of the development of concentric field loss, the risk of visual acuity deficits, the potential for progression of the lesions if therapy is continued, and the potential for progression once therapy has been discontinued.

Final Protocol Submission:	by August 2009
Study Completion Date:	by July 2016
Final Report Submission:	by September 2016

1526-3: A study examining the protective effect of taurine on vigabatrin-induced retinal damage in rodents, as reported by Jammoul *et al*. (Jammoul A F *et al*. *Ann Neurol* 65:98-107, 2009), but administering vigabatrin by the oral route. An attempt should be made to induce retinal toxicity in pigmented animals by, for example, exposing them to high intensity light for an appropriate duration following induction of mydriasis (cf. Rapp LM, Williams TP *Vision Res* 20:1127-1131, 1980). If this is successful, the study should be conducted in both albino and pigmented animals. The final study protocol should be submitted to the Agency for comment prior to study initiation.

Final Protocol Submission:	by January 2010
Study Completion Date:	by June 2011
Final Report Submission:	by November 2011

1526-4: An *in vitro* study to evaluate the ability of Sabril (vigabatrin) to induce CYP1A2 and CYP3A4 using methods described in the FDA Guidance for Industry: Drug interaction studies: Study Design, Data Analysis and Implications for Dosing and Labeling.

Protocol Submission:	by September 2009
Study Completion Date:	by April 2010
Final Report Submission:	by May 2010

Submit the protocol to your IND, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (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)).

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Sabril (vigabatrin) to ensure the benefits of the drug outweigh the risks of vision loss and of suicidal thoughts and behaviors.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Sabril (vigabatrin) 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 (vigabatrin). FDA has determined that

Sabril (vigabatrin) is a product for which patient labeling could help prevent serious adverse effects. Sabril also has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect their decisions to use, or continue to use, Sabril (vigabatrin). Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Sabril (vigabatrin).

We have also determined that a communication plan is necessary to support implementation of the REMS. The communication plan should be implemented at product launch (the first six months after product approval) and continued for three years.

Pursuant to 505-1(f)(1), we have also determined that Sabril (vigabatrin) can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate these risks listed in the labeling. The elements to assure safe use will mitigate the risk of Sabril (vigabatrin)-induced vision loss by ensuring that patients receive appropriate monitoring of vision, and by ensuring that Sabril (vigabatrin) therapy is discontinued in patients who experience inadequate clinical response.

Your proposed REMS, submitted on August 18, 2009, and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The REMS Assessment Plan should include, but is not limited to, the following:

1) Registration and drug distribution data

2) Medication Guide assessment data
   a) Patients' understanding of the serious risks of Sabril (vigabatrin)
   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

5) Patient/Parent or Legal Guardian Knowledge, Attitude and Behavior (KAB) Surveys

6) Ophthalmic professional KAB Surveys

7) Prescriber KAB Surveys

Additional details for the REMS assessment plan are in Appendix I.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(A), an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

The requirements for assessments of an approved REMS also include, in section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that 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 FDCA.

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

NDA 20-427 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 20-427
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 20-427
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

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

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert, Medication Guide). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 20-427."

IMMEDIATE CONTAINER LABELS

Submit final printed container labels that are identical to immediate container labels submitted on June 22, 2009 as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005). Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "Final Printed Container Labels for approved NDA 20-427." Approval of this submission by FDA is not required before the labeling is used.

PROMOTIONAL MATERIALS

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

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Tamy Kim, PharmD, Senior Regulatory Project Manager, at (301) 796-2250.

Sincerely,

{See appended electronic signature page}

Robert Temple, MD
Office Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Appendix I, Labeling and REMS

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

/s/

ROBERT TEMPLE
08/21/2009