

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-201

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-006

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 October 17, 2006, received October 18, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sabril (vigabatrin) for Oral Solution, 500 mg.

We acknowledge receipt of your additional correspondence and amendments dated:

| | | | |
|--------------------|-------------------|-------------------|-------------------|
| December 28, 2007 | February 12, 2008 | March 14, 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 |
| July 14, 2008 | July 17, 2008 | July 23, 2008 | August 4, 2008 |
| September 26, 2008 | October 31, 2008 | November 26, 2008 | December 24, 2008 |
| January 12, 2009 | January 30, 2009 | February 5, 2009 | February 24, 2009 |
| March 10, 2009 | March 25, 2009 | April 2, 2009 | April 9, 2009 |
| April 21, 2009 | April 24, 2009 | June 22, 2009 | July 7, 2009 |
| July 14, 2009 | July 29, 2009 | August 13, 2009 | August 17, 2009 |
| August 18, 2009 | August 19, 2009 | | |

The December 28, 2007, submission constituted a resubmission to our April 5, 2007, Refusal to File letter.

This new drug application provides for the use of Sabril (vigabatrin) for Oral Solution for Infantile Spasms.

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) (21U.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 indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because Sabril (vigabatrin) for Oral Solution for the treatment infantile spasms has an orphan drug designation, you are exempt from this requirement.

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 identify an unexpected serious risk of potential toxicity due to the increased plasma concentrations that may occur in younger infants, to assess a signal of a serious risk of neurotoxicity, or to assess the known serious risk of vision loss.

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:

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.

Final Protocol Submission: by July 2010
Study Completion Date: by September 2011
Final Report Submission: by March 2012

1523-2: A juvenile animal toxicity study of vigabatrin in a non-rodent species. The study protocol should be submitted to the Division for comment prior to study initiation.

Final Protocol Submission: by September 2012
Study Completion Date: by March 2014
Final Report Submission: by September 2014

1523-3: A study examining the protective effect of taurine on vigabatrin-induced retinal damage in rodent, 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

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of potential toxicity because of the increased plasma concentrations that may occur in younger infants.

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

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.

Final Protocol Submission: by January 2010
Study Completion Date: by July 2013
Final Report Submission: by March 2014

Submit the protocols to your IND for this product with a cross-reference letter to this NDA. Submit all final reports to this 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.

POSTMARKETING COMMITMENTS REPORTABLE UNDER SECTION 506B

We remind you of your postmarketing study commitment agreed to in your communication dated August 19, 2009. You commit to conduct the following:

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).

Final Protocol Submission: July 2010
Study Completion Date: July 2013
Final Report Submission: March 2014

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

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 22-006 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 22-006
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 22-006
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 22-006."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to carton and immediate container labels submitted on August 13, 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 Carton and Container Labels for approved NDA 22-006." 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.

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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

Appendix I: REMS Assessment Plan

- 1) Registration and drug distribution data
 - a) Report of Sabril (vigabatrin) 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 (vigabatrin) therapy before the beginning of the maintenance phase;
 - e) The number of patients whose therapy is interrupted because of 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 (vigabatrin) 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 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
 - 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 (vigabatrin) 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 (vigabatrin) use as well as analyses for the combined sample;
 - h) Level of understanding of Sabril (vigabatrin) 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) The number who opt out/ask to be removed from list;
 - ii) The 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 (vigabatrin); 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 you attempted to contact at each wave; of those you 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 and whether adult or pediatric practice;
 - (2) Experience with Sabril (vigabatrin); 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.