DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA APPROVAL

NDA 22-253
NDA 22-254

Schwarz Biosciences, Inc.
Attention: Alan Blumberg
Senior Director, US Regulatory Affairs
P.O. Box 110167
Research Triangle Park, NC 27709

Dear Mr. Blumberg:

Please refer to your new drug applications (NDAs) dated September 28, 2007, received September 28, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Vimpat (lacosamide) Tablets, 50 mg, 100 mg, 150 mg, and 200 mg, and Vimpat (lacosamide) Injection, 200 mg per 20 ml.

We acknowledge receipt of your additional submissions dated:

November 26, 2007	March 20, 2008	April 30, 2008	July 17, 2008	September 4, 2008
December 13, 2007	April 3, 2008	May 9, 2008	July 30, 2008	September 23, 2008
January 23, 2008	April 9, 2008	May 27, 2008	August 1, 2008	October 15, 2008
February 13, 2008	April 14, 2008	June 11, 2008	August 14, 2008	October 21, 2008
February 22, 2008	April 18, 2008	July 11, 2008 (2)	August 27, 2008	

These new drug applications provide for the use of Vimpat (lacosamide) as follows:

- Vimpat (lacosamide) Tablets as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older.

- Vimpat (lacosamide) Injection as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older when oral administration is temporarily not feasible.

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

Your applications for Vimpat (lacosamide) Tablets and Injection (NDA 22-253, 22-254) were not referred to an FDA advisory committee because your products are members of the class of previously approved anti-epileptic drugs and the products did not pose unique concerns beyond those applicable to other members of this class.

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 0 to 1 month for these applications because necessary studies are impossible or highly impracticable because there are too few children with partial onset seizures in this age group to study.

In addition, we are deferring submission of your pediatric studies in partial onset seizures for ages 1 month up to 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

1. Deferred pediatric studies under PREA for the adjunctive treatment of partial onset seizures in pediatric patients ages 1 month up to 17 years.

   Final Report Submission: July 2013

Submit final study reports to these NDAs. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated "**Required Pediatric Assessment.**"

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Title IX, Subtitle A, Section 901 of Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize 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)). This provision took effect on March 25, 2008.

In accordance with section 505-1 of the 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 Vimpat (lacosamide) 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 Vimpat (lacosamide). FDA has determined that Vimpat (lacosamide) has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use Vimpat (lacosamide). In addition, patient labeling could help prevent serious adverse effects related to the use of these products. Vimpat (lacosamide) may increase the risk of suicidal thoughts or behavior in patients taking anti-epileptic drugs for any indication. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Vimpat (lacosamide).

Your proposed REMS, submitted on October 17, 2008, in an electronic communication, is approved. The REMS consists of the Medication Guide included with this letter and the timetable for submission of assessments of the REMS included in your October 17, 2008 submission.

Prominently identify submissions containing 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:

- **NDA 22-253 & 22-254 REMS ASSESSMENT**
- **NEW SUPPLEMENT FOR NDA 22-253 & 22-254**
  PROPOSED REMS MODIFICATION
  < other supplement identification > [if included]
  <REMS ASSESSMENT> [if included]

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of FDAAA amends the FDCA to authorize 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), 21 U.S.C. 355(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 developmental neurotoxicity.

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

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following study:

2. A nonclinical study in rats to examine the effects of Vimpat (lacosamide) on brain development during the prenatal and early postnatal periods using more sensitive techniques for assessing central nervous system structure and function than were employed in the standard pre- and postnatal development study. You should consider the use of multiple daily dosing as a means of achieving higher plasma drug exposures during pregnancy and to better mimic the human exposure pattern.

The timetable you have submitted on October 28, 2008 states that you will conduct this study according to the following schedule:

Protocol Submission:	Within 6 months of approval
Final Report Submission:	Within 30 months of approval

Submit protocols to your IND 57,939 with a cross-reference letter to these new drug applications (NDA) 22-253 and 22-254. Submit final reports to your NDAs 22-253 and 22-254. Please use the following designators to label prominently all submissions, including supplements, relating to this postmarketing study 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

We acknowledge your written commitment to conduct the following postmarketing study as described in your submission dated October 28, 2008, as outlined below:

3. *In vitro* data to determine which enzymes may be involved in the metabolism of Vimpat (lacosamide) in addition to CYP2C19.

Final Report Submission:	within 18 months of approval

Submit the protocol to your IND (b) (4). Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to these NDAs. 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 these NDAs. 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 Study Commitment Protocol**
- **Postmarketing Study Commitment Final Report**
- **Postmarketing Study Commitment Correspondence**

HIGHLIGHTS WAIVER

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, 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 and 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 22-253 and NDA 22-254."**

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels 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 22-253 and NDA 22-254**" Approval of this submission by FDA is not required before the labeling is used.

In addition, we note your agreement on October 28, 2008 to address and make the following changes into your carton and immediate container labels:

General

(b) (4)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

(b) (4)

[redacted]

(b) (4)

[redacted]

(b) (4)

Marketing the products with FPL that is not identical to the approved labeling text including the changes noted above may render the product misbranded and an unapproved new drug.

CONTROLLED SUBSTANCE CLASS

We have recommended that this product be scheduled under the Controlled Substances Act. We remind you of the following statement that appears on the Form FDA 356h, "If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision." Once a final scheduling decision is made, your label must be amended to reflect the schedule.

EXPIRATION DATE (Injection)

We grant the proposed 36 month drug product expiry, when stored at controlled room temperature, for lacosamide 200 mg/20 mL injection packaged in 20 mL type I colorless glass vials with a grey rubber stopper coated with a (b) (4) and aluminum overseal.

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.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

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 Jacqueline H. Ware, Pharm.D., Supervisory Regulatory Project Manager, at (301) 796-1160.

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, M.D.
Deputy Director (Acting)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures (FDA Approved Labeling Text, Medication Guide, and REMS document)

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

/s/

Ellis Unger

10/28/2008 08:00:13 PM