



NDA 20-789/S-022 and S-025

Dainippon Pharmaceutical USA Corporation
Attention: Martina Struck, PhD
Senior Director Regulatory Operations
55 Challenger Road
Ridgefield Park, NJ 07660

Dear Dr. Struck:

Please refer to your supplemental new drug applications dated January 15, 2009, and March 26, 2009, received January 16, 2009, and March 27, 2009, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zonegran[®] (zonisamide) Capsules.

Reference is also made to our letter dated December 16, 2008, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for antiepileptic drugs. This information pertains to the risk of suicidal thoughts or behaviors. Although not a part of the safety labeling changes, we also requested that you add language pertaining to the North American Antiepileptic Drug (NAAED) Pregnancy Registry, if it was not already present. No other labeling change requests submitted to date are addressed in this letter.

This supplemental new drug application provides for revisions to the labeling for Zonegran consistent with our December 16, 2008 letter.

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

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on February 5, 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 20-789/S-022.**” Approval of this submission by FDA is not required before the labeling is used.

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, text for the 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 20-789/S-022."

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 becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

As stated in our December 16, 2008 letter, since Zonegran was approved in March 27, 2000, we have become aware of new safety information indicating an increased risk of suicidal thoughts and behavior with antiepileptic drugs (AEDs). An increased risk of suicidal thoughts and behavior was demonstrated in an FDA meta-analysis (dated May 23, 2008) of randomized, parallel-arm, placebo-controlled clinical trial data for 11 AEDs. In the meta-analysis, the odds ratio for suicidal behavior or ideation for all AEDs studied was 1.80 (95% CI: 1.24, 2.66); the estimated incidence of suicidal behavior or ideation was 0.43% among 27,863 drug-treated patients and 0.24% among 16,029 placebo-treated patients. This finding was generally consistent among drugs in the data analyzed. It was shared by drugs with varying mechanisms of action and was observed for all indications studied; this observation suggests that the risk applies to all AEDs regardless of indication of use. We consider this new analysis to be "new safety information" as defined in FDAAA.

The FDA's findings regarding AEDs and suicidal thoughts or behaviors were discussed at a joint Peripheral and Central Nervous System Drugs/Psychopharmacologic Drugs Advisory Committee Meeting on July 10, 2008. The Committee voted in favor of adding a section pertaining to this risk to the *Warnings* section of the prescribing information of all AEDs; the Committee also voted in favor of requiring a Medication Guide for all AEDs to inform patients of this increased risk.

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

Your previously approved patient package insert has been converted to a Medication Guide and has been revised to include the new safety information.

Your proposed REMS, submitted on January 15, 2009, and appended to this letter as amended, 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 March 26, 2009 submission.

Your assessment of the REMS should include an evaluation of:

- a. A survey of patients' understanding of the serious risks of Zonegran
- 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

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 20-789 REMS ASSESSMENT**
- **NEW SUPPLEMENT FOR NDA 20-789
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

If you do not submit electronically, please send 5 copies of submissions containing REMS assessments or proposed modifications of the REMS.

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 information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy 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).

If you have any questions, call Tamy Kim, PharmD, Regulatory Project Manager, at (301) 796-1125.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Labeling, Medication Guide 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/

Russell Katz

4/23/2009 10:37:14 PM