DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-789

MAR 27 2000

Elan Pharmaceuticals, Inc.
for Dainippon Pharmaceutical U.S.A. Corporation
Attention: Louise C. Johnson
Director, Regulatory Affairs
800 Gateway Boulevard
South San Francisco, CA 94080

Dear Ms. Johnson:

Please refer to your new drug application (NDA) dated March 19, 1997, received March 19, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zonegran (zonisamide) capsules.

We acknowledge receipt of your additional correspondence and amendments dated:

June 28, 1999	September 27, 1999	January 10, 2000	March 13, 2000
July 8, 1999	September 30, 1999	January 24, 2000	March 24, 2000
July 13, 1999	November 24, 1999 (2)	March 10, 2000	

Your submission of September 27, 1999 constituted a complete response to our June 30, 1999 action letter.

This new drug application provides for the use of Zonegran (zonisamide) capsules as adjunctive therapy in the treatment of partial seizures in adults with epilepsy.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

Labeling
The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert) and submitted draft labeling (immediate container and carton labels submitted November 24, 1999). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

We note that your September 27, 1999 submission advised that you currently plan to provide Zonegran commercially only in bottles of 100. However, given that this letter provides an approval action for this application, we are including reference to the bottles of 1000 and blisters of 100 in the HOW SUPPLIED section of the package insert given that these packaging configurations are provided for in this application. It is acceptable to remove references to the bottles of 1000 and blisters of 100 from your final printed labeling.

Additionally, we note that this application provides for one additional packaging configuration - a 28-count blister. This packaging presentation is not included in the HOW SUPPLIED section of the package insert because it is a professional sample, as you stated in your September 27, 1999 submission.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-789." Approval of this submission by FDA is not required before the labeling is used.

Clinical

1. For purposes of post-marketing surveillance, any hypersensitivity, skin, hematologic, and renal adverse event, as well as oligohydrosis, should be treated as unlabeled events. Any of these events determined to be serious should be submitted as 15-day written reports.

2. We urge you to create and maintain a registry of women who were exposed to Zonegran during their pregnancy. The value of this registry lies primarily in its capacity to prospectively enroll registrants before they are aware of fetal outcome. Our staff will be happy to discuss with you the specific design elements of this registry.

Expiration

The tentative expiration dating for Zonegran packaged in the 28-count [redacted] blister professional sample is 18 months at 25°C, and is based on the stability data provided in your September 27, 1999 submission.

Dissolution Method and Specification

We note that, in your March 10, 2000 submission, you agreed to the Agency's proposed dissolution method and specification for Zonegran 100 mg capsules as stated in our June 30, 1999 action letter.

Pediatric Studies

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the

requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies for adjunctive therapy in the treatment of partial seizures in pediatric patients until April 1, 2005. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver. We are waiving the pediatric study requirement for studies of adjunctive therapy in the treatment of partial seizures in pediatric patients less than 1 month of age.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Phase 4 Commitment

We remind you of your Phase 4 commitments specified in your submissions dated March 10, 2000, and March 24, 2000. These commitments are described verbatim below.

1. From your March 10, 2000 submission:
   "As discussed in the February 16, 2000 meeting between the Division and representatives of Elan Pharmaceuticals (Elan), Elan commits to perform a Phase 4 evaluation of the effects of zonisamide on ECGs.

We propose two approaches – the second approach will be taken only if the first approach is unsuccessful.

First Approach
As the Division suggested, we are investigating the possibility of retrieving the original ECG strips from Study 922. We have requested the original strips from the study sites, but have not yet received them. If we can obtain the majority of the original strips from the sites, we will provide them to an independent reader for analysis of the QT interval.

Because Study 922 collected ECG recordings only at baseline and at 24 months of therapy, there are no placebo-treated patients with 2 recordings available. The reader will be blinded to the timepoint of each recording. We propose to analyze the QT interval at 24 months compared to the baseline interval to detect any changes.

If we are successful in obtaining the original strips, we estimate the analysis can be completed by June 30, 2000.

Second Approach
In the absence of useful ECG information from Study 922, Elan commits to conduct a new study to evaluate the effect of zonisamide on ECG. This study would include evaluation of standard 12 lead ECG recordings by an independent, blinded reader. We have given some initial thought to the design of such a study and are still evaluating several important issues. These include

Inclusion of normal volunteers vs. patients with epilepsy
Measurement of ECG at steady state vs. following a single dose
Adequate sample size

We propose to submit a protocol outline to the Division if a new study is needed. Our expected timing for these activities is to determine the need for a new study (i.e., inadequate number of original strips from Study 922) by April 30, 2000. A protocol outline could then be submitted to the Division by May 31, 2000. We expect the study could be completed within a year of reaching agreement with the Division on the protocol. Thus, the earliest a final study report could be generated is June 30, 2001."

2. From your March 24, 2000 submission:

"As discussed in the March 21, 2000 teleconference between the Division and representatives of Elan Pharmaceuticals (Elan), Elan commits to perform a Phase 4 dose-response study.

This study design would include the following elements:
Randomized
Placebo or low dosage controlled
Parallel
Fixed-dose
Dose-response
Similar design to 912US
12 weeks double-blind comparison

We propose to submit a protocol to the Division by August 1, 2000. We expect the study could be completed in 18 months. Thus, we expect a final study report would be available August 01, 2002."

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Methods Validations
Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Promotional Material
In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Other
Please submit one market package (containers and cartons only) of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Jacqueline H. Ware, Pharm.D., Regulatory Management Officer, at (301) 594-2850.

Sincerely,

Robert Temple

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure