CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-789

APPROVAL LETTER

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,

/S/

APPEARS THIS WAY
ON ORIGINAL

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

Enclosure

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-789

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-789

JUN 30 1999

Elan Pharmaceuticals, Inc.
Attention: Louise C. Johnson
800 Gateway Boulevard
South San Francisco, CA 94080

Dear Ms. Johnson:

Please refer to your new drug application 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, 100mg.

We acknowledge receipt of your additional correspondence and amendments dated:

March 25, 1998	December 29, 1998	March 3, 1999
August 19, 1998	February 19, 1999	April 6, 1999
September 4, 1998	February 23, 1999	April 21, 1999
December 28, 1998	February 25, 1999	

Your submission of December 29, 1998 constituted a complete response to our March 19, 1998 action letter.

The User Fee goal date for this application is June 30, 1999.

We have completed the review of this application, as amended, and it remains approvable. Although you have made a major effort to re-examine safety and effectiveness data, as requested in the original Approvable letter, considerable additional work is needed before a definitive decision about its approvability may be made.

Specifically, before it may be approved, you will need to perform the additional analyses requested below. Many of these analyses are necessary because it appears that you have extensively revised the NDA database after discovering frequent errors in the original data on which our conclusions regarding safety and effectiveness, described in the Approvable letter, were based. Although you have stated explicitly that you have re-entered data for portions of the safety and all of the effectiveness database, you should confirm that you have done so for all the laboratory data submitted in the NDA. If you have not done this, we ask that you undertake a complete re-review of all laboratory data in the NDA, including a complete re-analysis of all laboratory data for the controlled trials, and submit complete reports (including an assessment of outliers) of your findings. Further, it is important that you submit the revised laboratory data sets for the controlled trials.

Before this application may be approved it will also be necessary for you to address the following:

SAFETY

1. Although your consultant originally concluded that zonisamide had an effect on the tubular secretion of creatinine, his re-analysis of the corrected data suggests that he has now concluded that it does have an effect on the GFR. Is this correct? Please provide a more detailed analysis of the randomized, controlled trial (RCT) data, as well as a more detailed discussion of the effects of zonisamide on renal function. Did other patients have the kind of progressive increases in creatinine/BUN that was seen in patients in Study 810-824? Please separately analyze patients with long-term exposure in the NDA for renal adverse events. Also ask the renal consultant to review the renal events reported from post-marketing experience in Japan. Finally, it may be necessary to propose a study to examine this effect in more detail, possibly as a phase 4 commitment.

2. With regard to the re-analyses of the laboratory data, for hepatic enzymes, specifically focus the outlier analysis on transaminases 3 times the upper limit of normal, and list all patients receiving drug or placebo who had increases of 3 times the upper limit of normal along with the corresponding bilirubin levels. This listing should be conducted separately for the RCTs and then the open experience and also for the Japanese Approval Cohort (JAC) and the Prospective Survey (PS).

3. Although you conducted a thorough search and analysis of skin rash in the NDA, there appeared to be no discussion of the effect of dose or the duration of use on the risk for rash. Please provide such a discussion for all experience, including that in the Japanese post-marketing experience (JPME). Also, your initial screen found 66 patients for review, but you were only able to retrieve 61 of their CRFs. Where are the remaining 5 patients' CRFs? We also note that your search was limited to the "primary database." Why is that?

4. In your evaluation of hematological events, you defined agranulocytosis too broadly by allowing patients with moderate-severe leukopenia to be counted. Use a standard definition from the literature (i.e, <600 neutrophil count) and provide a listing of cases from the NDA and from all Japanese experience. Include the duration of use and dose up to the time of the event. Use these findings to modify the description of the risk for agranulocytosis in labeling. Consider whether periodic WBC counts should be recommended in labeling.

5. We have several questions about the experience in the PS. Apparently, 271 patients who were enrolled in it did not have CRFs available for review. Please explain how this occurred. Were these patients not included because they dropped out of the study before 1 year? Compare the demographic characteristics of these 271 patients who did not have CRFs with those who did. In addition, we are concerned that there were very few serious events

identified in this study. Please provide the definition that was used to define serious. In addition, in that cohort, were all serious events to be reported (not just those thought to be drug-related)? Please review all AEs observed in the study applying the standard definition of serious AEs to determine the true incidence, and complete description, of these events in this cohort. Please also report the total amount of person-time in this study.

6. As requested in the first Approvable letter, please show the RCT adverse event tables separately for each RCT. The CNS events that you have re-coded should be included in each table, not in a separate table. CNS events will still require a warning statement.

7. There seems to be a systematic increase in alkaline phosphatase in the NDA, as well as in the JAC and PS, without any suggestion that SGPT increases. Please provide any information you have about the cause of the increase. Also please include an appropriate labeling statement describing this effect and provide suggestion for any further study.

8. Apparently, ECG interval data have not been entered into a database. Please enter and completely analyze these data (RCT and open data presented separately), if they are available. If these data are not available, please propose a phase 4 study to collect such data.

9. Please describe the pregnancy experience in the spontaneous reports separately for prospective and retrospectively reported events. A prospective report is one where the pregnancy is reported before there is any knowledge about fetal outcome. A retrospective report is one where pregnancy is reported only after fetal outcome is known.

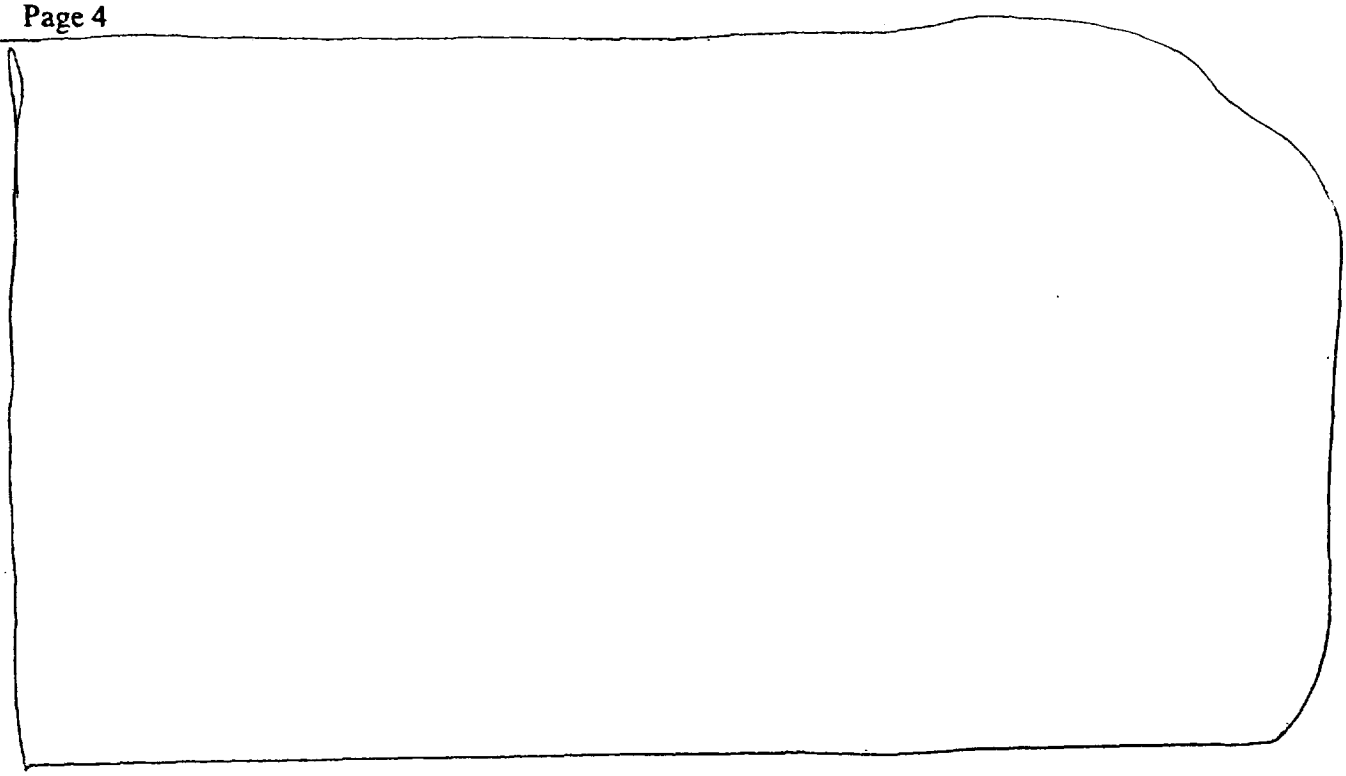
10. Please compute the rate of urinary calculi for the experience after 6 months of use and then for that experience of more than 12 months of use. Add these findings to labeling.

11. Describe and evaluate the cases of oligohydramnios that have been reported in the JPME. Please search the other data sources (NDA, other Japanese experience) to determine if similar cases occurred.

EFFECTIVENESS

As noted above, you have completely revised the data from the controlled trials and have concluded that there are no important differences between the results of the effectiveness analyses using these newly revised data and the original analyses. In order for us to independently confirm these conclusions, you must send us the complete, revised datasets on which these new analyses were based.

In addition, the number of pediatric patients 12 years of age or older enrolled in the controlled trials was insufficient to support a conclusion that zonisamide is effective in this population.



CHEMISTRY, MANUFACTURING, AND CONTROLS

1. The proposed expiration date of 36 months is acceptable for the drug product packaged in the bottles and blisters. However, it is recommended that the professional sample blisters have an expiration date not to exceed 12 months, based on the provided stability results. This 12 month expiration can be extended, if additional stability data (submitted post-approval) demonstrate comparability to the stability data generated with the blister.

2. The removal of the phrase "in a dry place and protected from light" from the label is unacceptable for the blister and blister professional sample. The storage should read as stated in our March 19, 1998 letter. The bottles (100 cc and 950 cc storage may read but the more complete phrase which includes is preferred.

LABELING

We have attached draft labeling to this letter. Although we have made a number of revisions to your proposed draft, this labeling must be considered extremely provisional, and can be expected to undergo significant revision based on the analyses requested above and on your responses to the requests embedded in the draft. Also, we may recommend development of a patient package insert.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

SAFETY UPDATE

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

PROMOTIONAL MATERIAL

As previously requested in our March 19, 1998 letter, 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

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with this Division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely yours,

/S/

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-789

MAR 19 1998

Athena Neurosciences, Inc.
Attention: Louise C. Johnson
800 Gateway Boulevard
South San Francisco, CA 94080

Dear Ms. Johnson:

Please refer to your new drug application dated March 19, 1997, received March 19, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zonisamide Capsules, 100mg.

We acknowledge receipt of your additional correspondence and amendments dated:

March 27, 1997	July 29, 1997	October 7, 1997	January 14, 1998
April 25, 1997	August 12, 1997	October 10, 1997	January 16, 1998
April 30, 1997	August 14, 1997	October 16, 1997	January 20, 1998
June 5, 1997	August 15, 1997	November 5, 1997	January 26, 1998
July 11, 1997	August 22, 1997	November 13, 1997	January 27, 1998
July 18, 1997 (4)	August 26, 1997	December 4, 1997	February 4, 1998
July 21, 1997	September 8, 1997	December 5, 1997	

The User Fee goal date for this application is March 19, 1998.

We have completed the review of this application as submitted with draft labeling, and it is approvable.

Although we have reached the general conclusion that the NDA may eventually be approved, additional work remains to be done. Specifically, until we have a clearer understanding of the nature, severity, and course of several of the adverse events associated with the use of zonisamide, as well as a more detailed understanding of the Japanese experience, we will be unable to write informative labeling for zonisamide. The steps needed to correct these deficiencies are described below.

In sum, before this application may be approved, it will be necessary for you to conduct further analyses, provide information, and agree to adopt as labeling for zonisamide, the draft labeling attached to this letter, which also contains detailed suggestions and requests.

Labeling

The attachment to this letter provides a draft of the labeling that the Agency asks you to adopt for zonisamide capsules upon its approval. Although sections of this proposal are taken verbatim from the labeling proposed by you in the NDA, other sections have been extensively revised and/or expanded to include new subsections. Please note that we have embedded throughout the text of the attached draft labeling, "Notes to Sponsor:", requesting further revisions or clarification of the label, as well as blank spaces requiring a numeric value which you must provide.

We have the following specific comments and requests for the following sections of labeling. This comprises a relatively small subset of the changes in labeling that we are requesting, but we felt that these deserved special attention.

1. Indications and Usage Section

   The attached draft labeling includes language in this section that permits a claim for zonisamide as adjunctive treatment for partial seizures in adults with epilepsy. The evidence and analyses presented in your NDA do not support a claim for an effect on secondarily generalized seizures for the reasons stated below.

   It is self-evident that the absolute incidence of an event that may only occur in the wake of some primary event (i.e., the definition of a secondary event) must be affected, if not entirely controlled, other factors held constant, by the incidence of the primary event. An antiepileptic treatment that is effective in reducing the absolute incidence of Partial Seizures [PS] can be expected, therefore, to reduce the absolute incidence of any seizure type that occurs only in the aftermath of a partial seizure. Accordingly, it might seem reasonable to allow a claim for an effect on secondary generalization on logical grounds alone.

   A claim for an effect on secondarily generalized seizures carries another inference, however: namely, that treatment reduces the probability of suffering a secondary generalized seizure in the aftermath of a PS. Whether or not this inference is true turns not on the absolute incidence of secondary seizures, but on the conditional risk of suffering a secondarily generalized seizure once a PS has occurred.

   It is conceivable that data of the kind required to evaluate this claim were collected during the conduct of your trials. If so, we would consider a claim for an effect of zonisamide on secondary generalized seizures, provided, of course, that the results of appropriate analyses support the claim.

To illustrate what we have in mind, consider the following analytic strategy. The proportion of PS suffered that were followed by a secondarily generalized seizure (of any type) would be calculated for both the baseline period and the experimental period for each individual. Then, for each study, the proportion of subjects under each treatment exhibiting a decrease in the proportion of PS with secondary generalization between baseline and experimental periods would be calculated. Support for a claim would turn on whether the reduction in proportion of secondary generalized seizures was significantly greater under zonisamide treatment than under the respective control conditions.

2. Warnings Section

a. General Statement: Given that zonisamide is chemically classified as a sulfonamide, we have added a general warning statement about sulfonamide adverse events to the draft labeling. This statement warns, in general, of serious and life-threatening events that have occurred with sulfonamide use, and similar language appears in other sulfonamide drugs.

b. Serious Rash: A number of serious rashes have been reported in association with zonisamide use. Please submit a comprehensive report of the occurrence of serious rash, defined as a rash that led to either discontinuation of treatment or hospitalization, or was diagnosed as Stevens Johnson Syndrome. It is critical that clear, comprehensive, and complete (including follow-up information) descriptions of each case be provided, where possible. When this information is unavailable, please describe what efforts you have undertaken to obtain complete information.

This report should present the data for the controlled trials (for drug and placebo groups) separately from that in open, uncontrolled experience. In the NDA database, the effect of dose on occurrence of serious rash should be examined, as should the time from the initiation of treatment.

Critically, we would also like to see included in this section a report of serious rash in the Japanese database, including an examination of the occurrence of serious rash in the prospective study, the retrospective survey, and the spontaneous reports separately. Also, a similar review of these events in the Japanese approval cohort of 1008 patients should be performed (we have additional comments about these data sources later in this letter).

Whenever possible, for the NDA database as well as for the Japanese data, rates of these events, in terms of number of events/patient-year, should be provided.

c. Serious Hematological Events: *Agranulocytosis/Aplastic Anemia* - We have asked you to draft separate sub-sections that describe the risk of occurrence of these two events. Please develop a case definition of these terms, and develop a comprehensive report of these events that is similar in form to that described above for Serious Rash.

d. Cognitive/Neuropsychiatric Adverse Events: Alterations in mental status, some so severe as to require discontinuation of zonisamide treatment, have been reported in association with its use. Our efforts to understand and describe the full panoply of untoward mental status and behavioral changes reported in association with the use of zonisamide have been severely hampered by the terminology employed. Terms such as confusion, thinking abnormal, even psychosis, convey little in the way of clinically useful information. To some degree, the problem is a generic one arising from the general limitations of COSTART as a dictionary for neuropsychiatric untoward events and phenomena.

Beyond the limitations of COSTART, however, are problems that arise because the strategy you employed for grouping and distributing untoward events among the various named categories of adverse events is unclear. In fact, we are concerned that events may have been misclassified (two examples of unclear classification are your terms "psychotic reaction" and "paranoid reaction"). To further illustrate, the differential diagnosis of altered mental status includes absences and absence status. This distinction is important because the treatment of the latter involves withdrawal, not incrementation, of zonisamide treatment.

Accordingly, a new analysis must be performed, and any review and analysis of events characterized by complex changes in behavior or mental status must make clear why one particular diagnostic assignment was made in preference to another, including an enumeration of the empirical findings supporting that choice (e.g., that an EEG done while the behavior was manifest showed a classic spike and wave configuration, etc.).

Clearly, extensive guidance regarding this effort cannot be provided in this letter, although the language we have included in the draft label should provide some explanation of our thinking and what we wish you to do. Staff of the Division of Neuropharmacological Drug Products , however, will be happy to meet with your staff to develop an appropriate strategy for the requested analysis.

3. Precautions Section

a. Kidney Stones: Based on the occurrence of kidney stones described in the NDA, we agree that a description of these events is warranted in zonisamide product labeling. However, in our review of the renal calculi data in Studies 920, 921, and 922, we could not follow the presentation of findings on renal calculi occurrence, and were unable to draft appropriate text for this section.

Accordingly, for the controlled trials and across the open experience in the development program, please discuss separately 1) those patients who were clinically symptomatic, breaking patients into those confirmed and not confirmed, 2) those patients who were asymptomatic but for whom renal calculi were detected by ultrasound, and 3) patients with echogenic foci that were not considered to indicate stones. Additionally, please separate patients with baseline findings from those with a normal baseline, and consider any available data relating dose or blood concentrations of zonisamide to the likelihood of stone formation. Lastly, based upon this discussion, we ask that you draft language regarding this event for inclusion in labeling.

4. Drug/Laboratory Test Interactions Section

In reviewing the available creatinine data from Study 810-924, we were struck by the unexpected, systematic elevation of creatinine in healthy volunteers that appeared to occur relatively early and continued to rise until the end of treatment, after which the mean approached baseline levels. Although there is a small increase in the mean creatinine in the zonisamide treated patients in the clinical trials, it is not consistent with the pattern seen in the Phase 1 study. For this reason, we are concerned that the finding in Study 810-924 may be the result of a drug-laboratory test interaction. Accordingly, to assist us in determining the effect of zonisamide on creatinine, please provide an explanation and comprehensive evaluation of the effect of zonisamide on renal function, including post-marketing surveillance data.

5. Adverse Reactions Section

As you can see in the draft label, we have asked you to extensively revise the Adverse Reaction Section. We do not believe it is yet clear that the adverse drug reactions (ADRs) from the three controlled trials are poolable, so we are asking you to draft, for review purposes, in effect, three separate subsections, each of which should be in the format you had originally proposed (e.g., initial text describing the most common ADRs, most common ADRs associated with discontinuation, controlled trial table [not necessary for 912EUR], etc.). It is, however, our intent to develop a single text and

table conveying these results, including any important variability, if possible. The Other Adverse Events Observed During Clinical Trials portion may include all data in the NDA database, and hence need occur only once.

6. Animal Toxicology Section

As per CFR 201.57(l), we have included this section at the end of labeling to describe liver abnormalities observed in dogs treated with zonisamide.

7. How Supplied Section

Please note that the storage statement is revised and reads as follows: "Store at 25°C (77°), excursions permitted to 15 -30°C (50-86°F) [see USP Controlled Room Temperature], in a dry place and protected from light."

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

In addition to the labeling issues noted above, we have the following requests.

Safety Issues

1. Hepatic Adverse Events

As discussed for the Serious Rash and Hematologic Events sub-sections, we are interested in a comprehensive discussion of serious hepatic events in the various datasources. As with the case for agranulocytosis and aplastic anemia, this discussion should begin with a case definition.

2. Safety Information from the Japanese Experience

You have informed us of considerable patient experience in Japan. We have only summary data from this experience, however, and, it has therefore not been possible to examine this data carefully or perform an independent review. At least two of these data sources appear to be prospectively followed cohorts, and, as such, might be capable of providing useful safety data.

For these reasons, we are requesting the following:

a. A full study report for the *Prospective Survey*, conducted in Japan, that elucidates its methods, (including the nature of the enrollment procedures [which patients were enrolled, etc.]) and the extent and nature of data capture and follow-up. Specifically, we request that you submit a patient listing of all dropouts and serious adverse events, narratives for events involving the hematologic, hepatic, renal, or skin systems, detailed follow-up information, and patient-time exposure information.

b. A full report on the 1008 patients in the Japanese Approval Cohort; specifically, a patient listing of all dropouts and serious adverse events, narratives for events involving the hematologic, hepatic, renal, or skin systems, a description of monitoring and follow-up procedures, and patient-time exposure data.

c. A re-evaluation of the spontaneous reports in Japan

   i) We are particularly interested in a detailed description of the methods you used to estimate the post-marketing exposure in Japan.

   ii) IRG Monitor Review - During our review, we found that there were differences in information described by the IRG reviewer compared with that in the adverse event report. Indeed, it was impossible for us to determine the methodology used by the IRG monitor to identify the cases that were chosen for further examination, and what information the monitor actually examined. Given this, please provide a detailed account of the methodology employed by the monitor to identify and re-assess cases of serious adverse events.

   Additionally, as requested in other sections of this letter, a re-evaluation of spontaneous reporting is needed for events in the hematologic, hepatic, renal, and skin systems.

3. Laboratory Data Clarifications

a. According to the individual study reports for the three randomized, controlled trials, three patients had clinically significant increases in creatinine, but when looking at the chemistry adverse event data, we were only able to locate one such patient. (This one patient appears to have had an increased creatinine reported due to a laboratory error.) Please locate the other two patients with

clinically significant increases in creatinine and provide the relevant clinical data.

b. Please provide clinical and laboratory data for patient [redacted]3201, who is reported to have had thrombocytopenia. We were unable to locate this information during our review.

c. In the individual study report of laboratory outliers, a patient is listed as having a hemoglobin of 3.9 gm/ml. We, however, were unable to locate this patient or any information on the laboratory value during our review. Please investigate this patient listing and provide additional information on this report.

4. Adverse Event (AE) Clarifications

a. Patient 912-201-358 was reported to have had moderately severe anemia, but the last reported hemoglobin of 6.9 gm/ml was not in the case report tabulations, nor was the corresponding white blood cell and platelet count reported. We would appreciate your providing any follow-up information or other clinical details on this patient.

b. Please describe the clinical nature of the gastrointestinal adverse events that appear to be associated with zonisamide.

c. Please provide a discussion of any cases of angioedema observed in the NDA development program. Individual patient information regarding these cases should be provided.

d. We note that patients in Study 922 reported an increased rate of cough. Please provide an explanation for this finding and any follow-up or clinical details for these patients.

5. Electrocardiogram (ECG) Data

In our review of this NDA, we were unable to locate a complete presentation of ECG findings. Were ECGs conducted in the phase 1 studies or in the randomized, control trials? If so, please provide a complete analysis of all ECG data separated by study. If no ECG data exist in the NDA, did the Japanese active-control trials collect such data? If so, please provide such data.

Safety Update

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

1. Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted vs now will certainly facilitate review.

2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Provide details of any significant changes or findings, if any.

4. Summarize worldwide experience on the safety of this drug.

5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

Dose Response

Available, limited data on dose-response suggest considerable activity at 100 and 200mg, yet most patients studied received considerably higher doses. Given the wide range of adverse effects of zonisamide, some possibly dose-related, we believe it is important to provide more informative dose-response information. Accordingly, we are seeking your commitment to carry out promptly a randomized, parallel, fixed dose, dose-response study, generally similar in design to the 912US study. It can be carried out in an add-on setting, needs to be about 6 weeks in duration, and should explore, at least, doses of 0 (placebo), 100, 200, and 400mg, with study of higher doses desirable.

Nomenclature

We have been advised by the CDER Labeling and Nomenclature Committee that two of your three proposed proprietary names, [redacted] are acceptable, whereas [redacted] is not. Accordingly, we request that you adopt, as the proprietary name for zonisamide capsules, one of these two names. This request is reflected in the attached draft labeling.

Biopharmaceutics

[redacted]

Chemistry, Manufacturing, and Controls

1. The expiration dating period for Zonisamide Capsules is 24 months when packaged and stored as per the original NDA submission.

2. Please submit zonisamide carton and container labeling (draft is acceptable) for our review.

Abuse Liability Issues

We remind you of your commitment to complete three abuse potential studies, as discussed during the July 28, 1997 telecon between members of the Agency [redacted] Accordingly, as part of your response to this letter, please submit the final study reports for these abuse potential studies for our review.

Additionally, upon submission of the final reports on the above studies, the Division of Anesthetic, Critical Care and Addiction Drug Products (HFD-170) requests your recommendation and justification for placement of zonisamide in a specific schedule of the Controlled Substances Act (CSA), based upon the data presented. Per 21 CFR 314.50(5) (vii), if a drug has a potential for abuse, a description and analysis of studies or information related to abuse of the drug, including a proposal for "scheduling" under the CSA, should be included in the NDA.

Promotional Material

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

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

Lastly, we have the following comments and suggestions. Although a response to these issues is not a requirement for approval, we would ask you to address them in your response to this letter.

Biopharmaceutics

1. Because zonisamide is extensively metabolized in the liver, we strongly urge you to conduct a conclusive pharmacokinetic study in hepatically impaired patients.

2. We recommend that you evaluate the role of N-acetyl transferase in the metabolism of zonisamide, as well as determining if zonisamide is metabolized by any cytochrome P-450 enzymes.

3. Because no information regarding the effects of zonisamide on oral contraceptives (or visa versa) was provided, we suggest that you conduct such a drug interaction study.

Pregnancy Registry

We urge that you create and maintain a registry of women who were exposed to zonisamide 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.

Pediatric Studies

We strongly urge you to perform adequate and well controlled investigations in children with epilepsy at the earliest possible time. Our staff will be happy to discuss appropriate study methodologies with you.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely yours,

/S/ 3/19/98

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