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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

5/21/01

Elan Pharmaceuticals, Inc.
For Dainippon Pharmaceutical U.S.A. Corporation
Attention:

Dear :

Reference is made to your Proposed Pediatric Study Request submitted on July 24, 2000 for Zonegran (zonisamide) capsules to .

To obtain needed pediatric information on zonisamide, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies:

Type of studies:
Study 1: Pediatric Efficacy and Safety Study (1 month to 16 years)
Study 2: Pediatric Safety Study (1 month to 16 years)
Study 3: Pediatric Pharmacokinetic Study (1 month to 16 years)

Indication to be studied (i.e., objective of each study):
Study 1: To establish the efficacy and short-term safety of zonisamide as adjunctive therapy in the treatment of partial seizures in pediatric patients ages 1 month to 16 years.

Study 2: To determine the long-term safety of zonisamide as adjunctive therapy in the treatment of partial seizures in pediatric patients, we request a two step evaluation. We ask that you first study pediatric patients ages 5 to 16 years, enrolling enough patients to ensure that approximately 100 are exposed to zonisamide for a minimum of 6 months. Once the long-term safety (see study endpoints) of zonisamide has been adequately ensured in this older pediatric population and the Agency concurs in this assessment, we ask that you study pediatric patients ages 1 month up to 5 years. You should enroll enough patients to ensure that approximately 100 are exposed to zonisamide for a minimum of 6 months.

Study 3: To determine the steady-state pharmacokinetics in pediatric patients ages 1 month to 16 years.

Age group in which study(ies) will be performed: .
Study 1, Study 2, and Study 3: 1 month to 16 years

For Study 3, we recommend that you conduct this study in two parts where you first study pediatric patients ages 5 to 16 years then study pediatric patients ages 1 month up to 5 years. Within these two age groups, we ask that you enroll a sufficient number of patients to adequately characterize pharmacokinetics of zonisamide and pediatric patients should be approximately uniformly distributed across each age range.

Study endpoints:
Study 1: A single standard measure of seizure frequency should be chosen as the primary outcome measure and standard measures of safety (clinical-including signs and symptoms- and laboratory).

Study 2: Appropriately frequent standard measures of safety (clinical – including signs and symptoms – and laboratory). Long-term safety assessment would include baseline cognitive/neuropsychiatric assessment and follow-up cognitive/neuropsychiatric assessments after six months of therapy and again approximately six months later. In addition, appropriate monitoring should be carried out to assess the drug specific safety concerns described on the next page.

Study 3: For the age group consisting of patients ages 1 month up to 5 years, a population pharmacokinetic study using sparse sampling approach (approximately 3-4 blood samples per patient in 3-4 time brackets instead of collection of blood samples at 3-4 fixed time points after the zonisamide dose) is recommended.

For the age group consisting of patients ages 5 to 16 year old children, the pharmacokinetic study in this age group could be either a traditional pharmacokinetic study (frequent sampling) or a population pharmacokinetic study using sparse sampling approach. If a sparse sampling approach is followed, the same principles described above for patients ages 1 month up to 5 years should be followed.

For studies in the age group defined zonisamide pharmacokinetic parameters including Cmax, tmax, AUC, t1/2 , CL/F and Vd/F should be calculated when possible. In addition, effects of covariates such as age, body-weight, body-surface area, gender and concomitant medications on zonisamide pharmacokinetic parameters such as apparent oral clearance (CL/F), apparent distribution volume (Vd/F) and elimination half-life should be studied.

Lastly, the effects of other concomitant anti-epilepsy drugs (AEDs) on the pharmacokinetics of zonisamide (and vice versa) should also be examined in pediatric patients.

Drug information:

Dosage form: Oral capsule for older pediatric patients or other age appropriate formulation for younger patients.

Route of administration: Oral

Regimen: To be determined by the development plan

Drug specific safety concerns:

Serious rash, serious hematologic events, oligohydrosis, hyperthermia, kidney stones, and effect on renal function.

Statistical information, including power of study and statistical assessments:

Study 1: Assessment of the between group difference on a standard measure of partial seizure frequency by a statistical methodology appropriate to the data generated and a descriptive analysis of the safety data. A sufficient number of pediatric patients to be able to detect a statistically significant difference between treatment and control should be included.

Study 2: Descriptive analysis of the safety data.

Study 3: Descriptive assessment of the effect of age on pharmacokinetic parameters.

Labeling that may result from the study(ies): Appropriate sections of the label may be changed to incorporate the findings of the studies.

Format of reports to be submitted: Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation.

Timeframe for submitting reports of the study(ies): Reports of the above studies must be submitted to the Agency on or before April 1, 2005. Please remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as **a new drug application or as a supplement to an approved NDA** with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the

beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call Jacqueline H. Ware, Pharm.D., Regulatory Project Manager, at 301-594-5533.

Sincerely yours,

Rachel Behrman, M.D.
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Rachel Behrman
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