HFD-104 Murphy

MAR 26 1999

IND (b) (4)
NDA 20-768

ZENECA PHARMACEUTICALS
ATTENTION: KEVIN MCKENNA, PHD
1800 CONCORD PIKE
PO BOX 15457
WILMINGTON, DE 19850-5437

Dear Dr. McKenna:

Reference is made to your Proposed Pediatric Study Request submitted on September 2, 1998 for Zomig (zolmitriptan) Tablets to IND (b) (4)

To obtain needed pediatric information on zolmitriptan, 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:

Types of studies:

Study 1: Adolescent Inpatient Safety and Tolerability Study if doses greater than (>) 5 mg are proposed for use.

Study 2: Pharmacokinetic Study

Study 3: Adolescent Efficacy Study

Study 4: Adolescent Long-Term Safety Study

Objectives/rationale:

Study 1: To evaluate the safety and tolerability of doses > 5 mg single doses of zolmitriptan in adolescents 12 to 17 years of age in an inpatient setting.

Study 2: To evaluate the pharmacokinetics of zolmitriptan in adolescents 12 to 17 years of age compared to adults.

Study 3: To evaluate the efficacy and safety of zolmitriptan in the treatment of adolescents 12 to 17 years of age with migraine headaches.

Study 4: To evaluate the long-term safety of zolmitriptan in the treatment of adolescents 12 to 17 years of age with migraine headaches.

Indication(s) to be studied:

The use of zolmitriptan tablets for the acute treatment of migraine headache in adolescents, ages 12 to 17 years.

Study design

Study 1: Randomized, double-blind, placebo-controlled, parallel group inpatient study in adolescents.

Study 2: Open label, single dose, parallel group inpatient pharmacokinetic study in adolescents and adults with history of migraine. Ideally, this study should be conducted during a migraine.

Study 3: Randomized, double-blind, placebo-controlled, parallel group outpatient study in adolescents.

Study 4: Open label, 12-month outpatient study in adolescents.

Age groups to be studied

Adolescent patients ages 12 to 17 years, inclusive.

Number of patients to be studied or power of the study to be achieved

Study 1: A sufficient number of adolescent subjects to be able to assess the acute safety of zolmitriptan at doses > 5 mg.

Study 2: A sufficient number of patients to adequately characterize the single dose pharmacokinetics of adolescents compared to adults.

Study 3: A sufficient number of adolescent migraine patients to be able to detect a clinically and statistically significant difference between treatment and control on a valid measure of headache response. The study should attempt to define the dose-response relationship in this age group, including the identification of a no-effect dose. There should be similar number of patients in the 12 to 14 and 15 to 17 age groups.

Study 4: A sufficient number of adolescent migraine patients to be able to characterize the long-term safety of zolmitriptan when used to treat multiple migraine attacks over one year. Each patient should treat, on average, 2 or more headaches per month. At a minimum, 300 to 600 patients, using the highest planned marketed dose, should be exposed for six months, and 100 patients, using the highest planned marketed dose, should be exposed for one year. There should be similar number of patients in the 12 to 14 and 15 to 17 age groups.

Entry criteria (i.e., inclusion/exclusion criteria)

Study 1: Adolescent subjects between 12 and 17 years of age with an average of 1 to 6 IHS defined migraine headaches per month.

Study 2: Healthy adolescent subjects between 12 and 17 years of age, and healthy adult subjects.

Study 3: Adolescent subjects between 12 and 17 years of age, with an average of 1 to 6 IHS defined migraine headaches per month.

Study 4: Adolescent subjects between 12 and 17 years of age, with an average of 1 to 6 IHS defined migraine headaches per month.

Clinical endpoints

Study 1: Appropriately frequent standard measures of safety, including acute cardiovascular safety.

Study 2: Pharmacokinetic measures as appropriate.

Study 3: The proportion of patients achieving a headache response at two hours, along with additional standard secondary migraine efficacy measures, and standard measures of safety (clinical—including signs and symptoms, and laboratory).

Study 4: Appropriately frequent standard measures of safety (clinical—including signs and symptoms, and laboratory)

Study evaluations:

Study 1: Inpatient safety data through 24 hours.

Study 2: Reports of relevant pharmacokinetic parameters for the doses described in labeling.

Study 3: Safety and effectiveness data through 24 hours.

Study 4: Safety data as discussed above through one year.

Drug information:

Dosage form: oral tablet

Route of administration: oral

Regimen: To be determined by the development program

Formulation: solid oral dosage form

Safety concerns: As previously discussed in prior communications, we have safety concerns regarding the use of higher than currently approved adult doses in this younger population. For this reason, study 1 (an inpatient safety and tolerability study) is requested.

Statistical information, including:

Study 1: Descriptive analysis of the safety data.

Study 2: Descriptive analysis of the pharmacokinetic parameters.

Study 3: Assessment of the between group difference on the proportion of patients achieving a headache response at 2 hours by a statistical methodology appropriate to the data generated.

Study 4: Descriptive analysis of the safety data.

Labeling that may result from these studies

INDICATON:

(b) (4)

CLINICAL PHARMACOLOGY: Pharmacokinetics: *Special Populations*:

Pharmacokinetic results from a pharmacokinetic study in adolescents non-migraineurs will be described.

CLINICAL PHARMACOLOGY: Clinical Studies:

Efficacy results from a double blind, dose ranging study in adolescent migraneurs will be described.

PRECAUTIONS: Pediatric Use:

The safety and effectiveness in pediatric patients (b) (4) have not been established.

ADVERSE REACTION: (b) (4)

(b) (4)

DOSAGE AND ADMINISTRATION: (b) (4)

(b) (4)

PATIENT INFORMATION: How to Use ZOMIG

Pending Results.

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 studies: Reports of the above studies must be submitted to the Agency on or before July 1, 2002. Please keep in mind that pediatric exclusivity only extends existing patent protection or exclusivity that has not expired a the time you submit your reports of the 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. We recommend you seek a written agreement, as described in the guidance to industry (*Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act)*, with FDA before developing pediatric protocols. 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 supplement to your 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 Lana Y. Chen, Project Manager, at 301-594-5529.

Sincerely yours,

Robert Temple 3/24/98

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

cc: IND (b) (4)
Archival NDA 20-768
HFD-120/division file
HFD-120/Chen
HFD-120/Levin/Oliva
HFD-120/Fitzgerald

HFD-860/Sahajwalla

HFD-101/Temple
HFD-600/Office of Generic Drugs
HFD-2/MLumpkin
HFD-104/DMurphy
HFD-6/KRoberts

Drafted by:
Initialed by:
Final:
filename: n:/chen/zomig pediatric request.doc

PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)