DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-001

Pharmacia and Upjohn Co.
Attn: Marcia Rogers
7000 Portage Road
Kalamazoo, MI 49001

Dear Ms. Rogers:

Reference is made to your Proposed Pediatric Study Request submitted on March 28, 2001 for Axert (almotriptan) to NDA 21-001.

To obtain needed pediatric information on almotriptan, 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: Pharmacokinetic Study

Study 2: Adolescent Efficacy Study

Study 3: Adolescent Long-Term Safety Study

Objectives/rationale:

Study 1: To evaluate the pharmacokinetics of almotriptan in adolescents 12 to 17 years of age with a history of migraine headaches.

Study 2: To evaluate the efficacy and safety of almotriptan in the treatment of adolescents 12 to 17 years of age with a history of migraine headaches.

Study 3: To evaluate the long-term safety of almotriptan in the treatment of adolescents 12 to 17 years of age with a history of migraine headaches.

Indication(s) to be studied:

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

Study design

Study 1: Single dose inpatient pharmacokinetic (PK) study in adolescents with a history of migraine headaches, ages 12 to 17 years. If possible, patients should be dosed during a migraine. The study design could be either a traditional PK design (frequent sampling) or a population PK study design

with sparse sampling approach. If a sparse sampling approach is used, blood samples should be obtained within time brackets and not at fixed time points, to cover the entire PK profile.

Study 2: Randomized, double-blind, placebo-controlled, parallel group outpatient study in adolescents with a history of migraine headaches. The study should attempt to define the dose-response relationship in this age group, including the identification of a no-effect dose. The protocol must allow the use of appropriate rescue medication after a suitable post-dosing interval. This efficacy study should not begin until the results of the PK study are known and submitted to the Agency. Should it result that exposures in adolescents are substantially higher than those seen in adults, then either a dose adjustment *(i.e.*, reduction) for the efficacy study might be necessary, or initial exposures to study drug in the efficacy trial may need to be performed under in-house conditions for safety reasons.

Study 3: Open label, 12-month outpatient study in adolescents with a history of migraine headaches.

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 migraine patients to adequately characterize the single dose pharmacokinetics of almotriptan (with a minimum of 18 for traditional PK study or a minimum of 50, with approximately 3 to 4 blood samples per patient, for a population PK approach).

Study 2: 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 efficacy. There should be similar number of patients in the 12 to 14 and 15 to 17 age groups.

Study 3: A sufficient number of adolescent migraine patients to be able to characterize the long-term safety of almotriptan when used to treat multiple migraine attacks over one year. Each patient should treat, on average, approximately 2 or more headaches per month for six to twelve months. 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 migraine patients between 12 and 17 years of age.

Study 2: Adolescent patients between 12 and 17 years of age, with an average of 1 to 6 IHS defined migraine headaches per month.

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

Clinical endpoints

Study 1: Pharmacokinetic measures as appropriate.

Study 2: The primary endpoint should be the proportion of patients achieving pain-free at a clinically appropriate time-point (two hours or less), or alternatively, the proportion of patients achieving a headache response at an appropriate time-point. Additional standard secondary migraine efficacy

measures and standard measures of safety (clinical—including signs and symptoms, and laboratory) should be included.

Study 3: Appropriately frequent standard measures of safety (clinical—including signs and symptoms, and laboratory)

Study evaluations:

Study 1: Reports of relevant pharmacokinetic parameters such as AUC, Cmax, oral clearance, terminal half-life etc. and comparison to PK parameters in adults.

Study 2: Safety and effectiveness data through 24 hours.

Study 3: 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

Statistical information, including:

Study 1: Descriptive analysis of the pharmacokinetic parameters and assessment of effect of age on PK parameters.

Study 2: Assessment of the between group difference on the primary endpoint by a statistical methodology appropriate to the data generated.

Study 3: Descriptive analysis of the safety data.

Labeling that may result from these studies: 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 studies: Reports of the above studies must be submitted to the Agency on or before July 1, 2004. Please remember that pediatric exclusivity extends only existing patent protection or exclusivity that has not expired or been previously extended 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 Lana Chen, Regulatory Project Manager, at 301-594-5529.

Sincerely,

{See appended electronic signature page}

Rachel E. 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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