CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-001

APPROVAL LETTER

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:

Please refer to your new drug application (NDA) dated December 17, 1999, received December 20, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Axert (almotriptan malate) tablets.

We acknowledge receipt of your submissions dated January 5, 2001, January 23, 2001, March 6, 2001, March 13, 2001, March 28, 2001, April 9, 2001 and April 30, 2001. Your submission of March 6, 2001 constituted a complete response to our December 20, 2000 action letter.

This new drug application provides for the use of Axert (almotriptan malate) tablets for the acute treatment of migraine.

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.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no 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 21-001." Approval of this submission by FDA is not required before the labeling is used.

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. In order that we may complete the methods validation process in an orderly fashion, please submit a corrected methods validation package. The necessary corrections were detailed in our fax of May 4, 2001.

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 note your March 28, 2001 submission includes your Pediatric Development Plan and Proposed Pediatric Study Request. That submission remains under review. We are deferring submission of your pediatric studies until approximately 2 years after approval.

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-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package 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 Lana Chen, R.Ph., Regulatory Management Officer, at (301) 594-5529.

Sincerely,

{See appended electronic signature page}

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

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-001

APPROVABLE LETTER

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:

Please refer to your new drug application (NDA) dated December 17, 1999, received December 20, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Axert (almotriptan) 6.25 mg and 12.5 mg tablets.

We acknowledge receipt of your submissions dated the following:

January 6, 2000	June 15, 2000	August 29, 2000
February 15, 2000	June 29, 2000	September 5, 2000
February 25, 2000	June 30, 2000	September 22, 2000
April 12, 2000	July 11, 2000	September 27, 2000
April 21, 2000	July 26, 2000	October 3, 2000
April 28, 2000	August 7, 2000	October 9, 2000
May 10, 2000	August 14, 2000	October 13, 2000
June 14, 2000	August 25, 2000	

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

CLINICAL:

1) We note that there is a discrepancy in the results of study M/31416/13/R as reported in the ISE and in the study report. In the ISE (Table 10, Item 8/10, Volume 91, page 28), you report a statistically significant difference between the 12.5 mg dose and placebo in favor of almotriptan. However, in the study report (Table 4.2.1.1.A, Item 8/10, Volume 15, page 35) the 95% confidence intervals for the placebo, 12.5 mg, and 25 mg groups clearly overlap, suggesting that the primary efficacy analysis was negative. Please explain this discrepancy.

   We also note that the on-site inspection of one of the clinical sites conducted between June 13 and June 15, 2000 revealed significant irregularities that places the data generated from

that center in serious doubt. We conveyed these findings to the investigator, Dr. Zintsch, in a letter dated August 8, 2000. As a result, we ask that you resubmit the primary protocol-specified analysis of this study that both includes and excludes the data from this center.

2) Please provide additional clinical information regarding Subject 756 in study CL25. The subject experienced clinically significant elevations in hepatic transaminases (AST/ALT) and total bilirubin while on chronic-intermittent treatment with almotriptan. This information should include a narrative summary, patient profile, and the case report form.

3) We note that, in study CL11, the 5 mg dose achieved a response rate of 66% compared to a placebo response rate of 42%. Although this comparison did not achieve nominal significance, it suggests that additional study of the low end of the dose-response curve may lead to successful development of a dose lower than 6.25 mg. We wish to discuss with you plans for such a study.

4) We note that, in general, the incidence of adverse events reported for the domestic long-term, open label study 0011 was greater than those reported for the European study CL25, raising the concern that events might have been under-reported in the European experience. Please submit a detailed description of the differences in the methodology used for the collection and reporting of adverse event data between the domestic and European experience.

5) Please re-analyze the blood pressure data from the appropriate Phase 1 and 2 to compare across groups the incidence of patients who meet appropriate "outlier" criteria.

CLINICAL PHARMACOLOGY:

1) The pharmacokinetics of almotriptan have not been assessed in patients with hepatic impairment. Based on the results of the ketoconazole interaction study, hepatic metabolism may play a larger role than previously suggested. Therefore, we recommend that you conduct a hepatic impairment study. Until the results of such a study are known, we are suggesting a reduction in dose in patients with hepatic impairment, as reflected in the Dosage and Administration section of attached labeling.

CHEMISTRY:

1) The synthesis flow chart (Section 4.1.3.1 of the original NDA submission) depicts a compound, designated as [redacted] as a starting material in the manufacture of almotriptan malate. We have determined that this material is not a starting material as defined by the Agency. Therefore, the methods for manufacturing and control of this material, as incorporated by reference to drug master file (DMF) [redacted] and additional documentation cited therein will be considered part of your application.

2) We have completed our review of the amendment to DMF [redacted] that was referenced in your amendment dated July 26, 2000. This DMF remains deficient. The DMF holder will be notified separately regarding the nature of the deficiencies.

3) The revised drug substance specification for almotriptan malate, provided in the June 30, 2000 amendment, is inadequate. We note the following:

4) [redacted]

5) The revised specifications for almotriptan malate tablets that were provided in the June 30, 2000 amendment are inadequate due to deficiencies in test procedures and insufficient information regarding some test methods. We note the following:

a) The revised analytical procedures do not include criteria for reporting of impurities (degradants) detected. Additionally, the specification should contain clear instructions regarding how total related substances are to be calculated.

b) The system suitability criteria you proposed in response to Items 8(d)(*i*) and 8(d)(*iii*) in the May 16, 2000 Information Request Letter are not adequate. Refer to our previous comments regarding suitability of these criteria for drug substance testing.

c) The dissolution test procedure is not adequately described in your application. A revised procedure was submitted in the June 30, 2000 amendment. The test procedure that was submitted does not contain instructions regarding sample volume, procedures

d) Item 8(m) of our Information Request letter requested that you provide the written analytical procedures that the analyst will follow. We have concluded, based on your response, that the request was not clear. To facilitate completion of our review, and methods validation by our laboratories, we request that you submit a copy of the current version of the quality control procedures that will be followed for release and stability testing. If necessary, an English translation should also be provided.

e) The revised specification for 12 mg tablets provided in Appendix 7 of your June 30, 2000 submission incorrectly indicates that the tablet imprint will be red rather than blue as stated elsewhere in the application.

6) Your response to Item 12 of the May 16, 2000 Information Request Letter indicates that all stability studies were performed using packaging components As you have provided no stability data to support use of

7) We have reviewed drug master file (DMF) cited in support of your application and determined that it is deficient for The nature of the deficiencies has been communicated to the DMF holder separately. When notifies you that the DMF has been updated, with a complete response to all items, please amend the NDA to reference the amendment.

8) Your response to Item 15 of the May 16, 2000 Information Request Letter states that the proposed 24 month expiration dating period is supported by stability data provided in the original submission and in the May 10, 2000 stability update. Please be advised that the Agency reviewed the stability data in the May 10, 2000 amendment prior to issuing the Information Request Letter. As we advised you previously, the primary stability data provided, which is limited to [redacted] long term data for the 6.25 mg tablet, will not support a [redacted] expiry. The maximum extrapolation beyond real time data that we will allow with a satisfactory statistical analysis and supportive stability is six months. Additionally, Agency statisticians we consulted do not consider your statistical approach to be valid. The shelf life predictions you obtained are not comparable to results obtained using the statistical approach recommended by the Agency. Our analysis of your 12.5 mg tablet potency data does not support a [redacted] expiration dating period. An expiry period of [redacted] is allowed.

9) Your June 30, 2000 submission proposes use of a red "A6" (stylized "A" over 6) imprint for 6.25 mg tablets and a blue stylized "A" for 12.5 mg tablets. The proposed imprint scheme is not acceptable.

10) Font size for established name on carton end flaps is too small relative to trademark on 6.25 mg and 12.5 six-count trade cartons and 12.5 mg six-count sample cartons.

11) Potency is not clearly visible on the 6.25 mg two-count sample carton, where it is printed in magenta on a teal background.

In addition, it will be necessary for you to submit revised draft labeling for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert, text for the patient package insert).

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

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. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same

format as the original NDA submission.

- Present tabulations of the new safety data combined with the original NDA data.

- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

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 requested a full waiver of these requirements in a letter dated October 7, 1999 submitted to your IND [redacted] for almotriptan. We have reviewed your arguments for waiver and do not concur with your conclusions; therefore, your request for a full waiver is denied as it does not meet the requirements for waiver under 21 CFR 314.55 (c) (2). Specifically, since migraine is a fairly common disorder in adolescents (ages 12 – 17), we believe that studies should be conducted to evaluate the usefulness of almotriptan in this population. Of particular note, we do not agree with your argument that existing OTC products intended to provide "symptomatic" relief from migraine attacks provide a sufficient alternative to treatment with a "triptan" class treatment for migraine.

Alternatively, we are prepared to defer submission of pediatric studies until approximately 2 years after approval of this application. However, in the interim, please submit your pediatric drug

development plans within 120 days from the date of this letter. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

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" 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.

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.

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, call Ms. Lana Chen, Project Manager, at (301) 594-5529.

Sincerely,

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