CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-016

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-016

Pfizer Inc.
Attention: Nancy Martin
50 Pequot Avenue
New London, CT 06320

Dear Ms. Martin:

Please refer to your new drug application (NDA) dated October 27, 1998, received October 27, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Relpax (eletriptan) 20 mg, 40 mg, and 80 mg tablets.

Reference is also made to our December 1, 2000 approvable letter.

We acknowledge receipt of your submissions dated the following: June 27, 2002, September 20 and 27, 2002, October 29 and 30, 2002, November 7, 20, and 27, 2002 and December 9, 17, 23 and 26, 2002.

The June 27, 2002 submission constituted a complete response to our December 1, 2000 action letter.

This new drug application provides for the use of Relpax (eletriptan) tablets for the acute treatment of migraine.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to, except for including the revisions listed, the enclosed labeling (text for the package insert, text for the patient package insert, immediate container and carton labels). These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as stated, in the product's labeling may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. 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. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission **"FPL for approved NDA 21-016."** Approval of this submission by FDA is not required before the labeling is used.

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will

work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. 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. 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". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

In addition, submit three copies of the introductory promotional materials that you propose to use for this/these product(s). Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert(s) directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Lana Chen, Regulatory Project Manager, 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:

21-016

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-016

Pfizer Inc.
Central Research Division
Attention: Larry M. Paglia, PhD
Eastern Point Road
Groton, CT 06340

Dear Dr. Paglia:

Please refer to your new drug application (NDA) dated October 27, 1998, received October 27, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Relpax (eletriptan) tablets.

Reference is also made to our October 27, 1999 approvable letter.

We acknowledge receipt of your submissions dated February 11; April 28; June 1; September 26; and October 13, 19, and 24, 2000. We also note that your submission of June 1, 2000 constituted a complete response to our October 27, 1999 action letter.

In addition, we refer to telephone conversations between the Agency and representatives of your firm on October 31, 2000 and November 1, 2000, in which we discussed the Agency's concerns about the potentially dangerous plasma eletriptan levels achieved with concurrent verapamil use. Finally, we refer to our facsimile of October 31, 2000 which provided our analysis of the maximum coronary artery constriction seen in each subject in Study 211.

We have completed the review of this application, as amended, and it is approvable. In the approvable letter dated October 27, 1999, we requested that you "document that the increased exposures (C_{max} and AUC) that result when eletriptan is given in conjunction with CYP3A4 inhibitors do not make the risk of such concomitant use unacceptable. This is critical because even though this concomitant use will be contraindicated in labeling, we cannot be confident that such use will not occur." We are not able to approve your application at this time because we believe that the information submitted in response to that letter fails to establish that the risk of such use is acceptable, particularly since eletriptan does not appear to offer any additional therapeutic benefit over currently approved triptans.

We note particularly that concomitant use of eletriptan with verapamil, a relatively commonly used CYP3A4 inhibitor in migraine patients, results in substantial increases in eletriptan exposure. In general, the eletriptan exposures achieved in that drug interaction study are substantially higher than the exposures that have been evaluated in the coronary angiography study (Study 211) yet that study suggests that even those plasma levels may be associated with clinically meaningful coronary vasoconstriction. We therefore remain concerned about the

potential effects of eletriptan on the coronary arteries, particularly at exposures achieved during CYP3A4 inhibition, but also at exposures associated with 40 mg and 80 mg single doses without metabolic inhibition. Before this application may be approved, therefore, it will be necessary for you to address the following:

You will need to conduct a placebo-controlled study designed to assess the potential of eletriptan to constrict coronary arteries at eletriptan concentrations that are higher than those achieved in Study 211 and that are comparable to exposures seen with CYP3A4 inhibition. The study should include several active controls of available triptans. The subjects studied should be those with suspected coronary artery disease who have been selected for diagnostic coronary angiography. We will be happy to discuss the design of the study with you.

Additionally, it will be necessary to revise the labeling that you propose. Attached is our draft labeling, much of which is subject to revision pending evaluation of additional data derived from the study described above.

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. 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.

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 Lana Chen, R.Ph., Regulatory Management Officer, at (301) 594-5529.

Sincerely

/S/

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

Attachment

19 page(s) of revised draft labeling has been redacted from this portion of the review.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-016

APPROVABLE LETTER 2

Chen

OCT 27 1999

NDA 21-016

Pfizer Inc.
Central Research Division
Attention: Nancy E. Martin
Eastern Point Road
Groton, CT 06340

Dear Ms. Martin:

Please refer to your new drug application (NDA) dated October 27, 1998, received October 27, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Relpax (eletriptan) 20 mg, 40 mg, 80 mg tablets.

We acknowledge receipt of your submissions dated the following:

Feburary 8, 1999	May 27, 1999	July 26, 1999
February 22, 1999	June 3, 1999	July 29, 1999
February 25, 1999	June 11, 1999	October 13, 1999
April 8, 1999	June 15, 1999	October 15, 1999
April 20, 1999	June 17, 1999	October 25, 1999.
April 27, 1999	June 25, 1999	

In addition, we refer to a telephone conversation between the Agency and representatives of your firm on August 24, 1999, in which we discussed the Agency's concerns about the occurrence of potentially dangerous plasma levels of eletriptan when it is given with inhibitors of CYP3A4. This concern was partly based on the results of a study in which elevated levels of eletriptan were seen when it was given concomitantly with erythromycin, a moderately potent 3A4 inhibitor. We further refer to your 10/25/99 facsimile submission of the preliminary results of Study 160-1045, which examined the effects of concomitant use of eletriptan and ketoconazole, a potent 3A4 inhibitor, and a telephone conversation with Agency staff on the same day.

We acknowledge that the preliminary results of Study 160-1045 suggest that the average Cmax of eletriptan is about 3 times and the AUC is about 6 times that when eletriptan is given alone (elevations of about 50% more than those seen with erythromycin). Given these results, we believe the NDA can eventually be approved with adequate labeling warning against the concomitant use of CYP3A4 inhibitors and eletriptan (see attached draft labeling). In addition, before we can approve the NDA, you will need to address the following issues:

1) You will need to submit a complete study report for Study 160-1045.

2) You will need to document that the increased exposures (Cmax and AUC) that result when eletriptan is given in conjunction with CYP3A4 inhibitors do not make the risk of such

concomitant use unacceptable. This is critical because even though this concomitant use will be contraindicated in labeling, we cannot be confident that such use will not occur. In particular, we are interested in your assessment of the effects on the cardiovascular system (e.g., hypertension, risk of coronary vasospasm, etc.) of the prolonged elevated exposure to eletriptan that will result from this interaction.

3) In addition, you will need to document, with evidence, the effects of the concomitant use of other CYP3A4 inhibitors on eletriptan plasma levels. We are interested here in identifying inhibitors that may be less potent than ketoconazole or erythromycin, with the goal of determining which ones, if any, need not be contraindicated as concomitant therapy with eletriptan.

4) You will need to submit the final results of the three long-term safety studies 108, 316 and 317 as well as any other available safety data. The report should contain the following information:

a. Completed study reports for studies 108, 316 and 317.
b. Integrated summary of these studies with special emphasis on:
    i. extent of exposures, including an update to table 2.8.2.13 in the NDA (this is the table that documents extent of long-term exposures by dose and documents compliance with ICH guidelines for long-term exposures)
    ii. deaths, adverse dropouts, serious adverse events
    iii. occurrence chest pain/pressure; neck/jaw pressure; and cardiac events
    iv. occurrence of elevated liver function tests
c. Patient narratives and case report forms of all deaths, adverse dropouts, serious adverse events, including cases of known or suspected cardiac ischemia, as well as cases with elevated ALT or AST > 3xULN or bilirubin > 1.5xULN.
d. Case Report Tabulations for studies 108, 316 and 317 in electronic format as SAS transport files.
e. The electronic datasets should include (but not be limited to) the following information:
    i. Dosing: the dataset should contain one row for each dose of medication taken, important variables are: patient identification, treatment assignment, attack number, date of study onset, date/time of dosing, study day of dosing (relative to study onset), amount of dose (in mg).
    ii. Adverse events: similar to the datasets provided in the NDA
    iii. Laboratory Data: the dataset should contain one row for each laboratory measurement. Important variables are – patient identification, treatment assignment, date of study onset, date/time of lab sample, date/time of last dose, amount of last dosage (in mg), study day of lab sample (relative to study onset), lab name (Sodium, ALT, Bilirubin, etc.), lab result, units, baseline lab result, lower limit of normal, upper limit of normal.

5) We note your October 13, 1999 response to our September 23, 1999 letter requesting 1) results from the learning and memory assessment study of the F1 generation and 2) repeat of the rat fertility study with higher doses to provide an adequate assessment of the potential effects of eletriptan on fertility. We remind you that the final study report of the learning and memory assessment study is still needed prior to approval. We have not changed our view that the rat fertility study should be repeated using higher doses. However, we can arrange a meeting to discuss the issues with you further.

6) 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 314.120. 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. We will be happy, of course, to arrange a meeting with you to further discuss the issues raised in this letter.

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 Lana Chen, R.Ph., Regulatory Management Officer, at (301) 594-5529.

Sincerely,

/S/

Robert Temple, M.D. — 10/27/99
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research