CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-269

APPROVABLE LETTER 2

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21269

Pfizer Inc.
Attention: Alan Dunbar
Director, Worldwide Regulatory Strategy
235 E 42nd Street
New York, NY 10017

Dear Mr. Dunbar:

Please refer to your new drug application (NDA) dated April 20, 2001, received April 20, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cardura XL (doxazosin mesylate) extended release tablets.

We acknowledge receipt of your submissions dated April 20, June 15 and 28, July 16, August 3 and 22, September 6, 2001, February 11, February 13, and your facsimile of February 21, 2002.

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 deficiencies:

1. There is inadequate information to determine the direct effect of a first dose of Cardura XL 4 mg on blood pressure and pulse, versus Cardura 1 mg, versus placebo, around the time of maximum plasma concentration.

2. There is inadequate information to directly compare the incidence of vasodilatory and cardiovascular adverse events between Cardura XL 4 mg and Cardura 1 mg after one day and after one week of therapy .

To address the above deficiencies the following is required:

1. Submit actual blood pressure and pulse data at periodic intervals over 24 hours after first dosing with Cardura XL 4 mg, compared with Cardura 1 mg, and with placebo. Conduct orthostatic maneuvers with blood pressure and pulse measurements.

2. Submit a critical analysis comparing clinical adverse events (especially those relating to vasodilation and orthostasis) between Cardura XL 4 mg and Cardura 1 mg in the first day and first week of therapy. This analysis may use all currently available data or may require new additional data from clinical trials in order to demonstrate non-inferiority of Cardura XL.

Additionally, the following deficiencies have been noted during the review of your NDA. We also request your response to these:

1. Provide all available safety information for the use of Cardura XL in black men or provide a justification why such information is not necessary.

2. Provide all available safety information for the use of Cardura XL in men older than 75 years of age.

3. Clarify why some data line listings for adverse events from the BPH pivotal trials listed 2 mg doxazosin

standard as the dosage strength administered during the first week of therapy as opposed to the per-protocol 1 mg dosage strength.

4. [redacted]

5. Submit revised labeling, highlighting that patients should not chew the GITS tablet, and highlighting that syncopal events have been reported to occur (albeit rarely) days or weeks after the start of therapy.

6. Submit pharmacokinetic data relevant to intra-subject daily variability from Phase 1 Studies DAZ-NY-96-007 and DAZ-NY-96-009.

7. Provide revised container labels that clearly differentiate the tradenames Cardura and Cardura XL.

Other revisions of the labeling may be required, including information relating to safety and effectiveness as this information becomes available.

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.

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 Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Acting Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
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/

Daniel A. Shames
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