CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-269

APPROVABLE LETTER 1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-269

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, August 3, September 6, 2001, February 11 and 28, May 10, 2002, December 17, 2003, April 2, May 14 and 18, and June 17, 2004.

The December 17, 2003 submission constituted a complete response to our February 22, 2002 action letter.

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 deficiency:

[redacted] impurities may form when [redacted] during the manufacturing process of the drug substance as well as the drug product. [redacted] are known genotoxins and potential human carcinogens.

To ensure patient safety, the Division requires a limit on the total concentration of [redacted] in the active pharmaceutical ingredient (API) and in the drug product. At this time no agreed-upon standard exists in the scientific community for limits on these specific impurities. Therefore, for this NDA, we require an interim standard of [redacted] for [redacted]

You have not demonstrated that the total amount of [redacted] in the API and the drug product is consistently [redacted]

To address the above deficiency, the following are required:

1. Demonstrate that your analytical method for detecting [redacted] is sensitive enough to detect [redacted]

2. Using a validated analytical method, provide data from the analysis of 12 batches each of the API, Cardura®, and Cardura XL® to confirm that the amount of [redacted] is indeed no [redacted]

In addition, it will be necessary for you to submit revised draft labeling as well as mock-up labels for container and cartons.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical 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 this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until the deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

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 Martin Kaufman, D.P.M., M.B.A., Regulatory Health Project Manager, at (301) 827-4234.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products (HFD-580)
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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