CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
19-787/S-007

Correspondence

FEB 26 1996

NDA 19-787/S-007

Pfizer Central Research
Medical Research Laboratories
Attention: William R. Murphy, Ph.D.
Eastern Point Road
Groton, CT 06340

Dear Dr. Murphy:

Please refer to your new drug application for Norvasc (amlodipine besylate) Tablets.

In reviewing your submission of April 25, 1995, our Medical Officer and Statistician have raised a number of questions that require your attention. Our concerns with your submission are detailed as part of this correspondence (see enclosure).

Sincerely yours,

/S/ 2/23/96

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure
Medical/Statistical Review of January 30, 1996

cc:
Original NDA
HFD-80/DDIR
HFD-110
HFD-110/Project Manager
HFD-110/DRoeder
sb/2/23/96

R 2.23.96

GENERAL CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-787/S-007

APR - 2 1996

Pfizer Central Research
Medical Research Laboratories
Attention: William R. Murphy, Ph.D.
Eastern Point Road
Groton, CT 06340

Dear Dr. Murphy:

Please refer to your new drug application for Norvasc (amlodipine besylate) Tablets.

In reviewing your submission of April 25, 1995, our secondary and tertiary medical reviewers have raised a number of questions that require your attention. Our concerns with your submission are detailed as part of this correspondence (see enclosure).

Sincerely yours,

/S/ 4/2/96

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure
Dr. Karkowsky's review of March 1, 1996
Dr. Lipicky's review of April 1, 1996

cc:
Original NDA
HFD-80/DDIR
HFD-110
HFD-110/Project Manager
HFD-110/DRoeder
dr/4/2/96

4-2-96

GENERAL CORRESPONDENCE

JUN 18 1996

Minutes of a Meeting Between Pfizer and the FDA

Date: May 28, 1996

Application: NDA 19-787/S-007
Norvasc (amlodipine besylate) Tablets

Sponsor: Pfizer

Subject: Labeling for CHF Supplement

Participants:

FDA

Robert Temple, M.D., HFD 101, Director, Office of Drug Evaluation 1
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
Juan Carlos Pelayo, M.D., HFD-110, Medical Officer
Wallid Nuri, Ph.D., HFD-710, Statistician
James Hung, Ph.D., HFD-710, Statistician

Pfizer

Robert Chew, Ph.D., Associate Director, Biometrics
Anne Cropp, Pharm.D., Global Candidate Team Leader
Allen Kraska, Ph.D., Group Leader, Clinical
William Murphy, Ph.D., Associate Director, Regulatory Affairs
Rita Wittich, Director, Regulatory Affairs
John Wolleben, Ph.D., Senior Vice President, Regulatory Affairs

Background

The supplemental application NDA 19-787/S-007 provides for labeling revised to incorporate data from the PRAISE trial regarding the safe use of amlodipine in patients with CHF. An approvable letter was issued on April 22, 1996. The sponsor requested a meeting to discuss labeling.

Meeting

Discussion

The sponsor's labeling proposals are identified by letters (A-J) in the margins of the attached draft. Each of these proposals was discussed in the meeting as follows:

A. The sponsor's proposal is acceptable.

B. The sponsor's proposal is acceptable.

C. The sponsor proposed that the description of cardiac morbidity be deleted. Dr. Wolleben believed that a description that breaks out the individual components of a combined endpoint would just invite people to look at the individual pieces, thus distorting the meaning of the study's findings. Dr. Temple disagreed. He said that clinicians need to know how cardiac morbidity is defined. The following text was agreed upon:

Draft

D. The sponsor proposed deleting the statement that there was [redacted] They argued that worsened heart failure was not considered to be an event unless it was the final event. In cases where it led to death, the endpoint was recorded as death. They believed that the study was not designed to be able to make such a comparison accurately. It was agreed that the sentence could be deleted.

E. The sponsor's proposal is acceptable, but the following text should be added to the end of their proposed sentence:

; the cardiac morbid events represented about _% of the total endpoints of the study.

F. The sponsor's proposal is acceptable.

G. The sponsor's proposal is acceptable.

H. This text should be revised as in "C" above. Delete [redacted]

I. The entire last sentence of this paragraph should be replaced with the following text (which is repeated from the **CLINICAL PHARMACOLOGY: Pharmacodynamics** subsection:

> Norvasc has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF.

J. The sponsor's proposal is acceptable, except they should delete [redacted] from the end of the paragraph.

Summary

The sponsor will submit final printed labeling based on the agreements outlined above.

Addendum

On May 29, 1996, Ms. Rita Wittich and Dr. William Murphy of Pfizer called and asked if they could delete the words "hospitalization for" in reference to worsened heart failure in the description of cardiac morbidity (see # 3 and #8 above). They pointed out that hospitalization

was necessary for any of the listed events to be classified as cardiac morbidity and that it would be misleading to use it only in reference to worsened heart failure. Dr. Temple considered their argument and decided that they should either change it to [redacted] or hospitalization for worsened heart failure" or keep the wording as agreed upon at the meeting.

Minutes preparer: /S/
David Roeder, HFD-110

Concurrence Chair: /S/
Robert Temple, M.D., HFD-110

Attachment

dr/6-3-96/6-18-96

RD: JHung/6-4-96
WNuri/6-4-96
JCPelayo/6-4-96
AKarkowsky/6-7-96
RTemple/6-14-96

cc: NDA 19-787
HFD-110
HFD-110/DRoeder/SBenton
HFD-101/RTemple

17 pages redacted from this section of the approval package consisted of draft labeling

RHPM Overview of NDA 19-787/S-007
Norvasc (amlodipine besylate) Tablets
March 26, 1996

Type: SE5

This supplemental application was submitted on April 25, 1995 and provides for the use of Norvasc as a "safe therapeutic option in the treatment of hypertension and/or angina in patients with congestive heart failure. "

Medical/Statistical Review
The pivotal investigation in this submission is considered to be the mortality/morbidity trial known as the PRAISE study (Prospective Randomized Amlodipine Survival Evaluation). There are nine other supporting trials. In their review dated January 30, 1996, Drs. Pelayo and Nuri state that the PRAISE study, at its inception, was an efficacy trial. The lack of results in support of an efficacy claim caused the sponsor to make the application a safety claim. Drs. Pelayo and Nuri did not come to a conclusion as to whether this application should be approved. They note that the data could be interpreted in conflicting ways. They point out the more patients in the amlodipine group than the placebo group had more peripheral edema , pulmonary edema and acute renal failure, but state that the latter two adverse events may be related to the fact that there were almost twice as many patients with deterioration of heart failure in the amlodipine group.

Medical Secondary Review
In his memo to Dr. Lipicky dated March 1, 1996, Dr. Karkowsky states, "Pfizer's development program was not successful in showing that Norvasc is helpful in mitigating symptoms or modifying morbidity/mortality in patients with congestive heart failure. Nevertheless, the experience with this drug in patients with CHF clearly demonstrates that Norvasc does no harm. Morbidity or mortality is not increased and exercise tolerance or quality of life does not deteriorate. Including this information would modify the tenor of the present labeling and is useful information for the practitioner." **See Dr. Karkowsky's labeling recommendations attached to the end of his review (pages 1-7).**

Clinical Pharmacology/Biopharmaceutics Review
In her review dated March 18, 1996, Dr. Parekh states, "CHF patients studied had higher amlodipine concentrations as compared to normals. Longer terminal half-lives were reflected in higher accumulation with once-daily administration. **The labeling for this population should appropriately reflect this observation."**

Environmental Assessment
In his review dated February 1, 1996, Dr. Zielinski states that a categorical exclusion from the requirement to prepare an Environmental Assessment applies to this supplement.

Division Director Memo
In his March 22, 1996 memo to Dr. Temple, Dr. Lipicky stated that PRAISE found no statistically significant effect with respect to its primary endpoint, morbidity/mortality, therefore, **he recommended specific labeling revisions reflecting PRAISE findings.**

RHPM Summary
Other than labeling, to my knowledge, there are no issues that would prevent action on this supplement.

Zelda McDonald, RHPM

for DR

cc: Orig. NDA
HFD-110
HFD-110/Roeder