CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
19-787/S-007

Approval Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUN 14 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 April 25, 1995 supplemental new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Norvasc (amlodipine besylate) Tablets, 2.5, 5, and 10 mg.

We acknowledge receipt of your correspondence and amendment dated May 1 and 22, and June 4, 1996. JR 6-20-96

The supplemental application provides for final printed labeling revised under the **CLINICAL PHARMACOLOGY** and ~~**WARNINGS**~~ PRECAUTIONS sections to include additional safety data regarding the use of Norvasc in patients with heart failure. The following changes were made:

The last paragraph of the **CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism** subsection was revised to read as follows:

> Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40-60%, and a lower initial dose may be required. A similar increase in AUC was observed in patients with moderate to severe heart failure.

The following paragraph was moved from the end of the **CLINICAL PHARMACOLOGY: Pharmacodynamics** subsection to follow the second paragraph of that subsection:

> In hypertensive patients with normal renal function, therapeutic doses of Norvasc resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

The entire text of the **CLINICAL PHARMACOLOGY: Studies in Patients with Congestive Heart Failure** subsection was replaced with the following paragraph:

> 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. In a long-term (follow-up at least 6 months, mean 13.8 months) placebo-controlled mortality/morbidity study of Norvasc 5-10 mg in 1153 patients with NYHA classes III (n=931) or IV (n=222) heart failure on stable doses of diuretics,

digoxin, and ACE inhibitors, Norvasc had no effect on the primary endpoint of the study which was the combined endpoint of all-cause mortality and cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure), or on NYHA classification, or symptoms of heart failure. Total combined all-cause mortality and cardiac morbidity events were 222/571 (39%) for patients on Norvasc and 246/583 (42%) for patients on placebo; the cardiac morbid events represented about 25% of the endpoints in the study.

The entire text of the **PRECAUTIONS: Use in Patients with Congestive Heart Failure** subsection was replaced with the following paragraph:

In general, calcium channel blockers should be used with caution in patients with heart failure. Norvasc (5-10 mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure (see CLINICAL PHARMACOLOGY) on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). 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.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling included in the June 4, 1996 submission. Accordingly, the supplemental application is approved effective on the date of this letter.

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, please contact:

Mr. David Roeder
Regulatory Health Project Manager
(301) 594-5313

Sincerely yours,

/S/

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

cc:
Original NDA
HF-2/MedWatch (with labeling)
HFD-2/MLumpkin (efficacy supplements only)
HFD-80 (with labeling)
HFD-101 (with labeling)
HFD-110
HFD-110/Project Manager
HFD-40 (with labeling)
HFD-613 (with labeling)
HFD-735 (with labeling)
HFD-21 (with labeling - for supplements discussed at advisory committee meeting)
DISTRICT OFFICE
HFD-222/New Drug Chemistry Division Director
HFD-110/DRoeder
sb/6/7/96
dr/6/10/96

6/13/96

RD: RMittal/6-10-96
RWolters/6-10-96
JCPelayo/6-10-96
WNuri/6-10-96
AKarkowsky/6-10-96
DRoeder/6-10-96

R 1 6/12/96

Approval Date: 31-Jul-92

JR 6-12-96
CM 6-13-96

APPROVAL

/S/ 6/13/96

/S/ 6/14/96

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NDA 19-787/S-007

APR 22 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 April 25, 1995 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Norvasc (amlodipine besylate) Tablets, 2.5, 5 and 10 mg.

The supplemental application provides for draft labeling revised under the **CLINICAL PHARMACOLOGY** and **WARNINGS** sections to include additional safety data regarding the use of Norvasc in patients with heart failure.

We have completed the review of this supplemental application as submitted with draft labeling. Before this supplement may be approved, however, it will be necessary for you to submit final printed labeling (FPL). The labeling should be identical in content to the enclosed marked-up draft. In addition, all previous revisions as reflected in the most recently approved package insert must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

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

Please submit sixteen copies of the printed labeling ten of which are individually mounted on heavy weight paper or similar material.

Within 10 days after the date of this letter, you are required to amend this supplemental 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 such action, FDA may take action to withdraw this supplemental application.

These changes may not be implemented until you have been notified in writing that this supplemental application is approved.

If you have any questions, please contact:

Mr. David Roeder
Regulatory Health Project Manager
(301) 594-5313

Sincerely yours,

/S/

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

Enclosure

cc:
Original NDA
HFD-2/MLumpkin (efficacy supplements only)
HFD-80
HFD-110
HFD-110/Project Manager
HFD-735/DBarash (with labeling)
HFD-100
HFD-110/DRoeder
sb/3/26/96;3/27/96;3/29/96
R/D: NMorgenstern/3/26/96 mam 3/29/96
ZMcDonald/3/27/96 3/29/96
FZielinski/3/27/96 3/29/96
RWolters/3/27/96 WN
WNuri/3/27/96 3/29/96
KMahjoob/3/28/9 Mahjoob 3/29/96
JPelayo/3/28/96 3/29/96
AKarkowsky/3/28/96

Approval Date: 7-31-92

APPROVABLE

3/29/96

4-1-96