CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19787/S009

ADMINISTRATIVE DOCUMENTS

Review of Labeling

NDA: NDA 19-787/S-009 Norvasc (amlodipine besylate) Tablets

Date of submission: August 14, 1995

Date of receipt: August 15, 1995

Applicant: Pfizer Inc.

Background: On March 22, 1995, we issued a supplement request letter to NDA 19-787, that stated:

"In reviewing the voluntary adverse drug reaction reports, we have found 10 cases of cholestatic hepatitis and 5 cases of elevated liver enzymes that were reported in association with the use of amlodipine. In our judgement, the association between reports of these adverse events and amlodipine use is too great to ignore, although (as is often the case in voluntary adverse drug reaction reporting) cause-effect is difficult to ascertain. Consequently, please revise the ADVERSE REACTIONS section of your package insert as follows:

Insert the following sentence after the third table of this section:

> Jaundice and hepatic enzyme elevations (mostly consistent with cholestasis) severe enough to require hospitalization have been reported in association with use of amlodipine.

Revise the penultimate paragraph of the ADVERSE REACTIONS section to read as follows:

> No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine."

Pfizer has submitted final printed labeling as a "Special Supplement - Changes Being Effected." This labeling went into effect in mid-September, 1995.

Review: The submitted final printed labeling has been revised as follows:

ADVERSE REACTIONS:
Rather than after the third table of this section, the following has been inserted above the last paragraph:

In the post-marketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine.

The placement of this information after information on the effect of changes to other laboratory tests seems reasonable. I will include a sentence in the approvable letter, asking the firm to insert commas around the clause "in some cases severe enough to require hospitalization" at the time of their next printing.

The following has been added to the formerly penultimate paragraph:

No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine.

Recommendation: I will prepare an approval letter for this supplement. It falls under 21 CFR 314.70 (c) (2)(i), Supplements for changes that may be made before FDA approval, to add or strengthen a contraindication, warning, precaution, or adverse reaction.

/S/ 11-17-95

Kathleen F. Bongiovanni for David Roeder

cc: 19-787/S-009
HFD-110
HFD-111/KBongiovanni/DRoeder
HFD-111/SBenton
kb/11/16/95.