CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19787/S009

CORRESPONDENCE

Regulatory Affairs Division
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NDA NO. 19-787 S-009

NDA SUPPLEMENT SLR

Inna Kissen, PhD
Associate Director—Drug Regulatory Affairs

August 14, 1995

Raymond Lipicky, M.D., Director
Division of Cardio-Renal
Drug Products (HFD -110)
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

RE: Norvasc (amlodipine besylate) Tablets
NDA # 19-787
Special Supplement - Changes Being Effected

Dear Dr. Lipicky:

Reference is made to your letter dated March 22, 1995 regarding Norvasc (amlodipine besylate) Tablets NDA #19-787 and to the telephone contact with Mr. D. Roeder on August 8, 1995.

Your letter stated that the Agency had received 10 reports of cholestatic hepatitis and 5 reports of elevated liver enzymes that were reported in association with the use of amlodipine. The Agency requested that the package insert labeling be revised to reflect this additional information in the Adverse Reactions section submitted as a supplemental application.

After a review of Pfizer's early alert safety database, we came to the conclusion to submit the changes in the Adverse Reactions section as a special supplement. The following statement is included in the Adverse Reactions Section of the amlodipine package insert above the last paragraph of this section:

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

ORIGINAL

As requested in your letter the penultimate paragraph of the Adverse Reactions section has been revised to read as follows:

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

Attached please find a copy of a safety report entitled "Amlodipine and adverse liver/biliary events" which contains the review of Pfizer's early alert safety database.

We are also submitting fifteen copies of the final printed labeling, ten of which are individually mounted. A highlighted copy of the Norvasc package insert is enclosed to facilitate review of the submission.

These changes will be placed into effect as of mid-September, 1995.

If you have any questions or comments please call my office at (212) 573-2503.

Sincerely,

I. Kissen

Inna Kissen, Ph.D.

IK:amw
Enclosure
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