CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19787/S002

CORRESPONDENCE

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Inna Kissen, PhD
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October 5, 1993

NDA NO 19-787 REF. NO. S-002

NDA SUPPL FOR SE8

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
5600 Fishers Lane
Rockville, Maryland 20857

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

Dear Dr. Lipicky:

Pursuant to 21 CFR 314.70 (c)(2)(i), we are herein submitting Special Supplement to the Norvasc Tablets (amlodipine besylate) NDA #19-787.

The Special Supplement consists of labeling changes in Adverse Reactions section. Additional adverse reactions are added to this section. In general, Adverse Reactions section is strengthen based on the original NDA data with the exception of gingival hyperplasia which was observed in Norvasc post-marketing experience. Changes in the Adverse Reactions section are as following:

1) old: "**Cardiovascular:** arrhythmia,....."

   new: "**Cardiovascular:** arrhythmia (including ventricular tachycardia and atrial fibrillation),....."

2) old: "**Gastrointestinal:** anorexia, constipation, dyspepsia", dysphagia, diarrhea, flatulence, vomiting."

   new: **Gastrointestinal:** anorexia, constipation, dyspepsia", dysphagia, diarrhea, flatulence, vomiting, gingival hyperplasia."

ORIGINAL

3) old: "Other reactions occurred sporadically in single patients and cannot be distinguished from concurrent disease states or medication."

new: "Other reactions occurred sporadically and cannot be distinguished from concurrent medications or disease states such as myocardial infarction and angina."

The above changes in Norvasc labeling are being effected as of October 5, 1993.

Twelve copies of the final printed labeling for Norvasc Tablets are enclosed.

If you have any questions, please do not hesitate to contact my office.

Sincerely,

I. Kissen

Inna Kissen, Ph.D.

IK:amw
Enclosure
norvasc2/6

CONFIDENTIAL/TRADE SECRET INFORMATION
SUBJECT TO 18-USC-1905 AND TO WHICH ALL
CLAIMS OF PRIVILEGE AND CONFIDENTIALITY
ARE ASSERTED IN BOTH STATUTORY AND
COMMON LAW.

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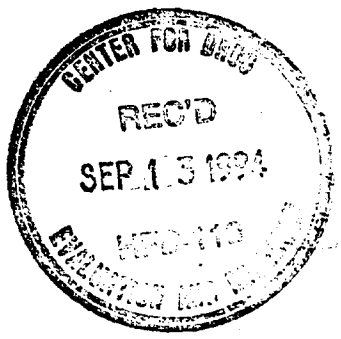
September 7, 1994

NDA SUPPL AMEND
(EM)
SLR-003



Raymond Lipicky, M.D., Director
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RE: Norvasc (amlodipine besylate) Tablets
NDA #19-787
Special Supplement

Dear Dr. Lipicky:

Please refer to our Special Supplement for Norvasc (amlodipine besylate) Tablets NDA #19-787, dated October 5, 1993 and to telephone contact with Mr. D. Roeder on October 25, 1993 regarding the above supplement.

FDA requested that we should elaborate on the inclusion of gingival hyperplasia and myocardial infarction and angina in the Adverse Reaction section of Norvasc labeling as stated in the October 5 supplement. In response to FDA request we prepared two reports on amlodipine and gingival hyperplasia (Enclosure I) and amlodipine and myocardial infarction/angina (Enclosure II). The Special Supplement was based on the data contained in these reports.

The report on gingival hyperplasia consists of a review of cases (Section I) and individual case reports (Section 2). As of January 31, 1994 there were three literature cases, and 18 were spontaneous cases reported directly to Pfizer.

Of these 21 cases, six are domestic cases. One case #9306804, was reported as a 15-day letter on March 9, 1994. The rest were non-serious cases of which two cases, #9306026 and #9306422, were submitted in periodic drug experience report on March 22, 1993, one case #9303705, was submitted in periodic drug experience report on September 7, 1993, and cases #9307080 and #9306941 were submitted in periodic drug experience report on May 23, 1994. All fifteen foreign cases were non-serious.

ORIGINAL

Based on the analysis of Pfizer's early alert safety database it would appear that amlodipine may be associated with gingival hyperplasia in some patients.

The labeling for Norvasc which was approved on July 31, 1992 contains the warning which states that rarely patients, particularly those with severe obstructive coronary artery disease, have developed increased frequency, duration, and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The approval of Norvasc labeling was based on the NDA database. This database consists of the original NDA #19,787 submitted on December 22, 1987, the 4-month Safety Update of April 29, 1988, Safety Update II of December 19, 1990 and Safety Update III of July 27, 1992. The NDA database includes 56 cases of myocardial infarction and 49 cases of angina. Of these cases, three cases of myocardial infarction and three cases of angina were evaluated as being related to amlodipine therapy.

The following review of the early alert safety database from April 24, 1992 (the cut-off date for Safety Update III) to March 29, 1993 identified 39 cases of myocardial infarction and 51 cases of angina. Among myocardial infarction cases, there were two clinical study cases where the event occurred shortly after starting amlodipine therapy and a possible association with the therapy could not be excluded. There were two spontaneously reported cases where the patients were taking amlodipine when their myocardial infarction occurred. Among angina cases, there were two clinical cases where the event occurred shortly after starting therapy and a possible association with amlodipine therapy could not be excluded. In two spontaneous cases, angina onset occurred shortly after starting amlodipine therapy, and a possible association with amlodipine could not be excluded. Thirty one cases of myocardial infarction and forty two cases of angina were attributed to progression of underlying cardiovascular disease. The rest of the cases were attributed to other causes (study-emerging illness, not temporally related or insufficient information).

Based on the amlodipine NDA, Safety Updates and Pfizer's early alert safety database, it was concluded that the majority of both the myocardial infarction and angina cases did not occur shortly after starting amlodipine, and were thought to be related to progression of underlying cardiovascular disease. Because of the nature of these events, it is difficult to distinguish them from underlying disease.

For this reason it was proposed in our October 5 submission that the statement in the Adverse Reactions section of the amlodipine labeling which stated that "Other reactions occurred sporadically in single patients and can not be distinguished from concurrent disease states or medication" should be modified to state that "Other reactions occurred sporadically and cannot be distinguished from concurrent medication or disease states such as myocardial infarction and angina". This revision of adverse reaction statement will strengthen and clarify safety information regarding amlodipine in addition to the information in the Warning section of the Norvasc labeling.

If you have any questions, please do not hesitate to contact my office.

Sincerely,

I. Kissen

Inna Kissen

IK:amw
Enclosure
norvasc2/3

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