DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FOI

TRANSMITTED VIA FACSIMILE

APR 24 1998

Rita Wittich
Director, Drug Regulatory Affairs
Pfizer Pharmaceuticals Group
Pfizer Inc.
235 East 42nd Street
New York, NY 10017

RE: **NDA#** 19-787
Norvasc (amlodipine besylate) tablets
MACMIS ID# 6566

Dear Ms. Wittich:

As part of its routine monitoring program, the Division of Drug Marketing, Advertising and Communications (DDMAC) has become aware of promotional materials for Norvasc (amlodipine besylate) tablets by Pfizer Inc. (Pfizer) that violate the Federal Food, Drug, and Cosmetic Act and its implementing regulations. Reference is made to a brochure (NX304V97), submitted under cover of Form FDA 2253. DDMAC has reviewed this brochure and has determined that it contains promotional claims that are false and/or misleading, and lacking in fair balance.

Misleading use of clinical studies to imply clinical benefit in patients with isolated systolic hypertension (ISH)

In this brochure, Pfizer uses quotations and results from clinical studies to suggest that Norvasc has clinical benefit in patients with ISH. However, **none** of these clinical trials examined Norvasc's effectiveness or safety in this patient population. The SHEP trials[1,2] studied the efficacy of chlorthalidone and atenolol. The Syst-Eur[3] trial results

1 SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. *JAMA*. 1991, 265:3255-3264.

2 Kostis JB, Davis BR, Cutler J, et al. for the SHEP Cooperative Research Group. Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension. *JAMA*. 1997,278: 212-216.

and the JNC VI[4] quotation are based on treatment with nitrendipine, a calcium channel blocker not approved for use in the United States. Because Norvasc was not studied in these trials, its clinical benefit is not known for patients with ISH. Therefore, Pfizer's appropriating the results of these clinical trials to imply the same or similar clinical benefit in patients receiving Norvasc therapy is misleading. Promotional claims for clinical benefit of Norvasc must be based on substantial evidence derived from adequate and well-controlled clinical trials in which Norvasc was the drug studied.

Misrepresentations of efficacy

On page 4, Pfizer presents supine blood pressure reductions in older and younger patients in a graph. However, the resultant decrease in supine blood pressure presented in this graph is much greater than demonstrated in clinical trials that evaluated Norvasc's efficacy. The approved product labeling for Norvasc describes a trough placebo-corrected reduction in supine blood pressure to average about 13/7 mm Hg (systolic/diastolic). Therefore, DDMAC considers this graphic presentation to be misleading because it overstates Norvasc's efficacy and is inconsistent with the approved product labeling.

Misrepresentations of dosing and administration

On page 4, Pfizer claims that Norvasc provides "[c]onsistent, continuous blood pressure control, even if a dose is missed." This claim is based on the results of a clinical trial comparing the antihypertensive effect of amlodipine (n=15) versus enalapril (n=15), for up to 48 hours after a patient's last dose.[5] DDMAC has determined that this study is inadequate to provide a substantial basis for the claim. In addition, the implication that it is acceptable to miss doses of a medication used to treat hypertension, a chronic condition, is inconsistent with the Dosage and Administration section of Norvasc's approved product labeling, and is a message that may undermine the optimal treatment of patients.

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3 Staessen JA, Fagard R, Thijs L, et al. *Randomised double-blind comparison of placebo and active* treatment for older patients with isolated systolic hypertension. *Lancet*. 1997, 350:757-764.

4 The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Archives of Internal Medicine*. 1997, 157:2413-2446.

5 Hernandez-Hernandez R, Armas de Hernandez MJ, Armas-Padilla MC, et al. The effects of missing a dose of enalapril versus amlodipine on ambulatory blood pressure. *Blood Pressure Monitoring*. 1996, 1:121-126.

Misrepresentations of indications and usage

On page 5, Pfizer presents the results of a clinical trial in patients with congestive heart failure (CHF).[6] In this clinical trial, Norvasc had no effect on the primary endpoint of the study (the combined endpoint of all-cause mortality and cardiac morbidity), on NYHA classification, or on symptoms of heart failure. Yet, Pfizer concludes that "Norvasc has a comprehensive safety profile, even in patients with severe CHF," implying that Norvasc can be used safely in these patients. However, Norvasc is not indicated for use in patients with CHF. Therefore, DDMAC considers this presentation to be misleading because it is inconsistent with the approved product labeling for Norvasc.

Lacking in fair balance

In this multiple page brochure, on page 6, Pfizer presents "headache (which was not different than placebo) and edema" as the most common side effects associated with use of Norvasc. However, Norvasc is associated with several other common and/or dose-related side effects, including fatigue, dizziness, flushing, and palpitation, which are not presented. Since promotional materials must present information about the risks associated with the use of the drug in a manner reasonably comparable to that of claims concerning the drug's efficacy, DDMAC considers this presentation to be lacking in fair balance.

DDMAC notes that the promotional claims presented in this brochure are also presented in several other promotional pieces for Norvasc. Pfizer should immediately cease distribution of this brochure and all other promotional materials for Norvasc that contain the same or similar claims or presentations. Pfizer should submit a written response to DDMAC, on or before May 8, 1998, describing its intent and plans to comply with the above.

Pfizer should direct its response to the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds Pfizer that only written communications are considered official.

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6 Packer M, O'Connor CM, Ghali JK, et al. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. *N Engl J Med.* 1996, 335:1107-1114.

In all future correspondence regarding this particular matter please refer to MACMIS ID #6566 in addition to the NDA number.

Sincerely,

Janet Norden, MSN, RN
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications