DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FOI

TRANSMITTED VIA FACSIMILE

Ellen R. Westrick
Senior Director
Office of Medical/Legal
Merck & Co., Inc.
Sumneytown Pike
West Point, PA 19486

JUN - 4 1998

RE: NDA#20-386/20-387
Cozaar (losartan potassium) tablets and
Hyzaar (losartan potassium-hydrochlorothiazide) tablets
MACMIS ID #6572

Dear Ms. Westrick:

As part of its routine monitoring program, the Division of Drug Marketing, Advertising and Communications (DDMAC), has become aware of promotional materials for Cozaar (losartan potassium) tablets and Hyzaar (losartan potassium-hydrochlorothiazide) tablets by Merck & Co., Inc. (Merck) that violate the Federal Food, Drug, and Cosmetic Act and its implementing regulations. Reference is made to the following materials submitted under cover of Form FDA 2253: journal ad [981621(1) 904/803-COZ], and slim jim [981322(1)-05-COZ]. DDMAC has reviewed these promotional materials and determined that they promote Cozaar and Hyzaar in a manner which is considered false or misleading because they contain unsubstantiated patient compliance claims.

Reference is made to DDMAC's letter, dated August 9, 1995, that provided comments on Merck's proposed computer based detailing program that contained patient compliance claims. In that letter, DDMAC addressed these same or similar issues concerning the use of data from retrospective prescription refill records for patient compliance claims, and determined that they were not adequate to support these claims.

Currently, in the journal ad and slim jim, Merck uses the results of two retrospective audits of prescription refill records to support claims of superior patient compliance for Cozaar and Hyzaar. The first one-year retrospective audit (Audit #1) compares the percentage of antihypertensive patients remaining on a new prescription of Cozaar or Hyzaar for a 12-month period versus the percentage of antihypertensive patients remaining on a new prescription of Norvasc (amlodipine besylate), Procardia XL (nifedipine), Lotensin (benazepril hydrochloride), Tenormin (atenolol), or hydrochlorothiazide. The second one-year

retrospective audit (Audit #2) compares the percentage of patients remaining on a new, initial prescription of Cozaar or Hyzaar for a 12-month period versus the percentage of patients remaining on a new, initial prescription of an ACE inhibitor, calcium channel blocker, beta blocker, or diuretic. For both audits, compliance is defined as a patient who remained on therapy during the 12-month period, based on prescription refill data.

DDMAC has reviewed these promotional materials and has determined that they are misleading because these prescription record audits are not adequate to support a superior patient compliance claim for Cozaar or Hyzaar. Specific objections to these materials are as follows:

- Merck's patient compliance estimates based on prescription refills do not provide an accurate description of actual compliance with therapy. For example, if patients switched to another pharmacy or provider, these patients would be considered "noncompliant" and counted as patients who discontinued therapy. However, these patients may have remained on therapy and merely utilized another pharmacy or provider.

- In Audit #1, in a comparison of Cozaar/Hyzaar to Norvasc, Procardia XL, Lotensin, Tenormin, or hydrochlorothiazide, Merck does not account for patients who may have switched to a generic product or another branded product. For example, patients taking Procardia XL may have switched to generic nifedipine or to another branded nifedipine product. Merck would count these patients as discontinuations of therapy, which would be inaccurate.

- In Audit #2, patients were excluded if it appeared that they were taking antihypertensive medications for reasons other than hypertension. However, Merck's strategy for exclusion of nonhypertensives would not necessarily eliminate those patients taking ACE inhibitors, calcium channel blockers, etc., for reasons other than hypertension. Therefore, this audit may have included patients who were not "hypertensive" by diagnosis.

- The following claims, "[s]ignificantly more patients remained on Cozaar for one year" and "[t]he initial antihypertensive patients stayed with longer" suggest that lack of patient compliance was the only reason for discontinuation of therapy. However, physicians often discontinue patients' therapy for a variety of reasons, including lack of efficacy, intolerability, etc., so this implication is misleading.

- Although Merck provides a disclaimer stating that these compliance comparisons do not establish superiority of Cozaar/Hyzaar over other agents or that patients were well-controlled and tolerating therapy at one year, presentation of this disclaimer does not correct the misrepresentations of the data from these two audits. Patient compliance may be influenced by a number of factors, including patient variables (e.g., motivation, memory,

etc.), economic variables, drug-related variables (e.g., complex dosing regimens, intolerable side effects), etc. Therefore, Merck's definition of patient compliance, (i.e., a measure of time that a patient remained on therapy, based on retrospective prescription refill audits) does not address or measure these factors.

In light of the limitations of Merck's data described above, these promotional materials are misleading because they contain patient compliance claims that are not supported by adequate evidence. Merck should immediately cease distribution of these and other similar promotional materials for Cozaar and Hyzaar that contain the same or similar claims or presentations. Merck should submit a written response to DDMAC on or before June 18, 1998, describing its intent and plans to comply with the above.

Merck 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 Merck that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #6572 in addition to the NDA numbers.

Sincerely,

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