DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

DEC 22 1998

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

RE: NDA#20-386/20-387
Cozaar (losartan potassium) tablets and
Hyzaar (losartan potassium-hydrochlorothiazide) tablets
MACMIS ID #7337

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 regulations. Reference is made to the following materials submitted under cover of Form FDA 2253: brochure [986247(1)-11-COZ], and slim jim (986278-11-COZ). DDMAC has reviewed these promotional materials and determined that they promote Cozaar and Hyzaar in a manner which is considered false and/or misleading because they contain unsubstantiated efficacy and safety claims, and are lacking in fair balance.

Use of pharmacokinetic data to imply clinical advantages

In the above referenced pieces, Merck presents claims concerning Cozaar's and Hyzaar's pharmacokinetic profile, as follows:

- The A-II blocker with a unique pharmacokinetic profile
- The ONLY A-II blocker with both a rapid, active parent...And a potent, long-acting metabolite

These claims imply that losartan possesses clinical advantages due to its pharmacokinetic profile. However, the pharmacokinetic profile of losartan, including its active parent and metabolite, has not been shown to provide a clinical advantage over other antihypertensive therapies with different pharmacokinetic profiles. Therefore, presentation of these claims

based on pharmacokinetics are misleading because they imply a clinical advantage, including suggesting clinical superiority, when no such clinical relevance has been demonstrated by substantial evidence.

Misrepresentations of mechanism of action

In these promotional materials, Merck presents the tagline "unique in A-II blockade" concerning Cozaar's and Hyzaar's mechanism of action. This claim implies that the mechanism of action of Cozaar and Hyzaar provides clinical advantages over other angiotensin II receptor blockers. Although the angiotensin II receptor blockers have differences in receptor binding affinity, this characteristic has not been shown to have clinical relevance. Therefore, presentation of this mechanism of action claim is misleading because it suggests clinical effect, including implying clinical superiority, when no such clinical relevance has been demonstrated by substantial evidence.

Misleading claims for metabolic effects

Merck presents the following claims concerning Cozaar's effect on serum uric acid:

- Cozaar is the only A-II blocker that has an effect on serum uric acid levels
- losartan provided a small decrease during chronic administration
- Hypertension management should not negatively impact other conditions associated with cardiovascular risk...["elevated serum uric acid" is listed under this claim].

The approved product labeling (PI) for Cozaar states that "there was a small uricosuric effect leading to a minimal decrease in serum uric acid (mean decrease < 0.4 mg/dL) during chronic oral administration." However, this small uric acid lowering effect has not been shown to provide a greater clinical benefit than an antihypertensive therapy that has no effect on serum uric acid levels. Furthermore, this presentation implies that elevated serum uric acid levels are a cardiovascular risk factor, which has not been demonstrated by substantial evidence. Therefore, this presentation is misleading because these claims overstate the clinical importance of losartan's effect on serum uric acid and imply a greater clinical benefit than demonstrated by substantial evidence. In addition, when coupled with the claims that imply that elevated serum uric acid levels are a cardiovascular risk factor, this presentation suggests that losartan's small uricosuric effect may lower cardiovascular risks, which is not supported by substantial evidence.

Unsubstantiated superiority claims for tolerability

Merck presents the claim that losartan possesses "superior tolerability with respect to edema." Beneath this claim, Merck presents two graphs that depict the incidence of "drug-related"

edema from two clinical trials. The first trial (Study #1) compared losartan (monotherapy or in combination with hydrochlorothiazide) to nifedipine GITS, and the second trial (Study #2) compared losartan (monotherapy or in combination with hydrochlorothiazide) to amlodipine (monotherapy or in combination with hydrochlorothiazide). In addition, Merck presents a significant p value for the comparison of edema for the drug therapies stated above. DDMAC has reviewed this presentation and has determined that it is misleading for the following reasons:

- Presentation of "drug-related" adverse events is misleading because the subjective investigator-rated occurrence rates may not reflect the actual occurrence of edema. In fact, in both studies, the actual occurrence rates of edema were higher than the investigator ratings. Therefore, this presentation is misleading because it minimizes the occurrence of this adverse event and implies that Cozaar/Hyzaar are more tolerable than demonstrated in the clinical trials.

- Study #1, a comparison of losartan (monotherapy or in combination with hydrochlorothiazide) to nifedipine GITS monotherapy alone, is not adequate to evaluate the incidence of edema because hydrochlorothiazide is known to decrease edema. Therefore, this presentation is misleading because it implies that Cozaar/Hyzaar are associated with a lower incidence of edema than nifedipine GITS, which is not based on substantial evidence.

- The reprints providing support for these claims do not adequately address whether edema was a pre-specified endpoint. Therefore, these studies may not be adequately designed to evaluate the incidence of an individual adverse event rate, and the cited p value may not be interpretable.

- These claims imply that Cozaar/Hyzaar are superior to both nifedipine GITS and amlodipine with respect to the incidence of edema. However, these studies are not adequate to support this implication for each product. Therefore, the implication that Cozaar/Hyzaar are superior to either nifedipine GITS or amlodipine is misleading because it is not supported by substantial evidence.

Lacking in fair balance

In these materials, Merck presents dosing recommendations for Cozaar/Hyzaar and numerous claims concerning their beneficial clinical effects in differing patient populations. However, Merck fails to present information from the warning section of the PIs concerning the risk of hypotension in volume-depleted patients. Therefore, this presentation is lacking in fair balance because it fails to present information concerning an important risk associated with the use of Cozaar and Hyzaar, implying that their use is safer than demonstrated by substantial 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 January 8, 1999, describing its intent and plans to comply with the above. In its letter to DDMAC, Merck should include the date on which these and other similarly violative materials were discontinued.

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 #7337 in addition to the NDA numbers.

Sincerely,

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