DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

OCT 28 1999

Preeti I. Pinto, M.S., M.T. (ASCP)
Quality Assurance Liaison Leader
AstraZeneca, LP
725 Chesterbrook Blvd.
Wayne, PA 19087-1000

RE: NDA #20-838
Atacand (candesartan cilexetil) Tablets
MACMIS ID #8297

Dear Ms. Pinto:

As part of its routine monitoring program, the Division of Drug Marketing, Advertising and Communications (DDMAC) has become aware of promotional materials for Atacand (candesartan cilexetil) tablets by AstraZeneca, LP (AZ) that violate the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. Reference is made to selected promotional materials for Atacand, including a slide kit (160122) and a brochure (160323), submitted under cover of Form FDA 2253. DDMAC has reviewed these materials and has determined that they contain promotional claims that are false or misleading.

Unsubstantiated Superiority Claims

In the slide kit, you present claims and representations from your "CANDHY" (CANDesartan cilexetil vs enalapril vs HYdrochlorothiazide) clinical trial[1] that imply that Atacand is superior to enalapril or hydrochlorothiazide. For example, in a graph, you compare the reduction of blood pressure in women receiving either once-daily doses of Atacand (8 mg to 16 mg), enalapril (10 mg to 20 mg), or hydrochlorothiazide (12.5 mg to 25 mg). The graphic representation of the results from this trial depicts that Atacand reduced blood pressure to a greater degree than enalapril or hydrochlorothiazide (HCTZ). In the text beneath the slide, you present the following claim:

> Atacand (8 mg and 16 mg) exerted statistically significantly greater antihypertensive efficacy than enalapril (10 mg and 20 mg), and HCTZ (12.5 mg and 25 mg) after 12 weeks' treatment (P=.01, P<.001, respectively).

1. Referenced as Data on File, DA-ATA12.

Your claims and presentations clearly imply that Atacand is superior to enalapril and HCTZ. However, this clinical trial is inadequate in design to support claims of superiority for Atacand over enalapril or HCTZ. Claims or representations of superiority over another drug product must be based on substantial evidence derived from adequate and well-controlled clinical trials. Therefore, DDMAC considers claims of superiority of Atacand over enalapril or HCTZ derived from this clinical trial, to be misleading because they are not based on substantial evidence. Furthermore, your disclaimer that "these results have not been confirmed in a second study," does not adequately correct the misleading promotional messages made by presentation of this data.

DDMAC notes that this same violation was cited our untitled letter, dated November 23, 1998, with respect to your presentation of superior efficacy claims for Atacand over losartan.

Misleading comparisons

In the brochure, you present a table of across-label comparisons of the "Pharmacologic Profile" of Atacand, versus Cozaar (losartan), Diovan (valsartan), Avapro (irbesartan), and Micardis (telmisartan). Your presentation misleadingly implies that Atacand possesses clinical advantages over these other products based on various pharmacological characteristics. For example, in the "interactions with food" category, you present a "no" for Atacand, but a "yes" for Cozaar and Diovan. You further present a note, from the Pharmacokinetic sections of the approved product labeling (PI) for Cozaar and Diovan, that states that food decreases absorption (Cozaar), bioavailability (Diovan), and peak plasma concentration (Cozaar and Diovan). However, the Dosage and Administration section of the PIs for each product state that both Cozaar and Diovan "may be administered with or without food." Therefore, the implication that Atacand possesses a clinical advantage over the other products listed in this table, based on pharmacokinetic properties, is misleading because the clinical relevance has not been demonstrated by substantial evidence. These misleading implications are not limited to your presentation of food interactions, but include the other characteristics compared in this table, such as cytochrome P450 metabolism.

Graphic misrepresentations

In the brochure, you present a graph depicting the dose-response reduction of systolic blood pressure (SBP) and diastolic blood pressure (DBP) for Atacand 16 mg and 32 mg from a clinical trial.[2] The mean difference in BP reduction between the two groups, based on this "per protocol" analysis, was 3.5 mm Hg (DBP) and 4 mm Hg (SBP). However, your graph is entitled "44%

2. Reif M, White WB, Fagan TC, et al. Effects of Candesartan Cilexetil in Patients with Systemic Hypertension. *Am J Cardiol.* 1998;82:961-965.

greater reduction in DBP in a dose-response study comparing 16 mg to 32 mg," and a similar claim is presented in the summary of Atacand benefits, under the header "Power in BP reduction." On the graph, you have labeled that Atacand 32 mg resulted in a 44% greater reduction in DBP and a 37% greater reduction in SBP. Your presentation of percent differences between the groups is misleading because it distorts and misrepresents the actual differences, implying much larger difference than what was actually demonstrated. In addition, promotional materials in which you present the claim (e.g., "44% greater reduction in DBP in a dose-response study comparing 16 mg to 32 mg"), without the graph, are also misleading.

AZ should immediately cease distribution of these promotional materials, and all other promotional materials for Atacand that contain the same or similar claims or presentations. AZ should submit a written response to DDMAC, on or before November 12, 1999, describing its intent and plans to comply with the above. In its letter to DDMAC, AZ should include a list of all promotional materials that were discontinued, and the discontinuation date.

AZ 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-42, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds AZ that only written communications are considered official.

In all correspondence regarding this matter, please refer to MACMIS ID #8297 in addition to the NDA number.

Sincerely,

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