DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

F.O.I

TRANSMITTED VIA FACSIMILE

Nancy A. Price
Associate Director
Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

SEP 23 1999

RE: NDA# 20-665
Diovan (valsartan) Capsules
MACMIS# 7893

Dear Ms. Price:

As part of its routine monitoring program, the Division of Drug Marketing, Advertising and Communications (DDMAC), has become aware of promotional materials for Diovan (valsartan) capsules by Novartis Pharmaceuticals Corporation (Novartis) that violate the Federal Food, Drug, and Cosmetic Act (Act) and its regulations. Reference is made to the following materials, submitted under cover of Form FDA 2253: "Val-HeFT Slide Kit and Reference Guide" (DIO-3013), physician/patient brochure (Starter program, DIO-C-8501), "ARB flashcard" (DIO-1031), and patient brochure (Medication switch, DIO-8037). DDMAC has reviewed these promotional materials and has determined that they promote Diovan for unapproved uses, contain false or misleading comparative claims, and lack fair balance.

Unapproved uses

The approved product labeling (PI) for Diovan states that it is indicated for the treatment of hypertension, and that it may be used alone or in combination with other antihypertensive agents.

In the "Val-HeFT Slide Kit and Reference Guide," you present information about an on-going clinical trial (Val-HeFT: Valsartan in Heart Failure). DDMAC has reviewed this slide kit and has determined that it contains claims suggesting benefits and uses of Diovan that are not based on substantial evidence, but rather on pilot studies or on current on-going investigations. For example:

Slide 10 contains claims and representation concerning Diovan's role in the reduction of left ventricular hypertrophy (LVH). The header states that "Valsartan reduces left ventricular hypertrophy," and is followed by presentation of a graph that depicts a greater mean reduction in

left ventricular mass index for valsartan (n=29), than for the comparator drug, atenolol (n=29). In the text that corresponds to this slide, you state:

> Potential applications for valsartan in the field of cardiovascular therapy extend beyond control of blood pressure. Although left ventricular hypertrophy (LVH) may occur as a response to pressure overload in hypertension, it is in itself a factor for cardiovascular morbidity and mortality independent of the level of arterial pressure...

This presentation implies that Diovan is useful for reducing LVH, and therefore, useful for decreasing cardiovascular morbidity and mortality. Furthermore, this presentation implies that Diovan is superior to atenolol based on these findings. However, the clinical significance of reducing LVH, including its long-term impact on reducing cardiovascular morbidity and mortality are unknown. Therefore, these implied benefits and uses for Diovan, including its implied superiority over atenolol, are misleading because they are not based on substantial evidence. Although you present a statement in the text following the slide that "The clinical effects of this are unknown," this disclaimer does not adequately correct the messages made by presentation of this slide and the corresponding text.

Slide 11, entitled "Valsartan in CHF," presents claims and representations related to Diovan's use in patients with congestive heart failure (CHF). You present on the slide that "Pilot studies demonstrate favorable results," followed by statements that valsartan improved hemodynamic parameters in patients who did not receive angiotensin converting enzyme inhibitors (ACEIs), and that valsartan augmented the hemodynamic and hormonal effects of ACEI therapy in patients who did receive ACEIs. This presentation implies that Diovan is useful for the treatment of CHF. However, these pilot studies are inadequate to support the implied indication for Diovan's use in the treatment of congestive heart failure. Therefore, this presentation promotes Diovan for an unapproved use.

Slides 23 and 24 provide a description of Val-HeFT "substudies" and "expectations." For example, the text following slide 23 states:

> These substudies are expected to provide additional information as to the potential of valsartan to favorably affect the remodeling process, offer protection in terms of morbidity and mortality, and improve symptoms and the quality of life for patients with heart failure.

However, this affirmative, overreaching statement, coupled with your conclusively stated study "expectations" on slide 24, create a misleading impression of the anticipated efficacy of Diovan in patients with CHF, when in fact, the Val-HeFT study is incomplete. Therefore, this slide kit makes representations and suggestions for uses of Diovan that are not approved.

False or misleading comparisons

Promotional materials are misleading if they contain a drug comparison that represents or suggests that a drug is safer or more effective than another drug when it has not been demonstrated to be safer or more effective by substantial evidence, generally in the form of adequate and well-controlled, head-to-head, clinical trials. The information contained in the following four promotional labeling pieces include false or misleading statements or suggestions that Diovan is safer or more effective than other drug products. These claims are not supported by substantial evidence.

1. **Val-HeFT Slide Kit and Reference Guide**

   In the "Val-HeFT Slide Kit and Reference Guide," you present claims that state or imply that Diovan is superior to atenolol. As stated above, these claims and implications are misleading because they are not based on substantial evidence.

2. **Physician/Patient Brochure (Starter Program)**

   This "Starter Program" physician/patient brochure is designed to be separated, with a section for the physician, the patient, and the pharmacist. In the section for the physician, you present the claim "When side effects jeopardize your patient's therapy,". . . "Unlike losartan and irbesartan, Diovan does not seem to be metabolized by the CYP 450 system." This presentation implies that Diovan, because of its metabolic properties, is associated with fewer side effects than losartan or irbesartan. However, this implication of clinical superiority is false or misleading because no such clinical benefit has been demonstrated by substantial evidence.

3. **Angiotensin II Receptor Blockers (ARB) Flashcard**

   In the "ARB flashcard," you present across-label comparisons of valsartan (Diovan), losartan, irbesartan, and candesartan cilexetil. These comparisons imply that valsartan: (1) is superior to losartan and irbesartan because it is not metabolized by the CYP 450 system; and, (2) is superior to losartan and candesartan cilexetil because it is not a pro-drug. As stated above, however, these claims are misleading because they imply that valsartan possesses clinical advantages due to its metabolic properties, when no such clinical relevance has been demonstrated by substantial evidence.

   Furthermore, in the "ARB flashcard," you present conclusions from a variety of studies in a manner that misleadingly implies that the data were obtained from direct comparisons of the products described. In particular, you present the efficacy results from several clinical trials for individual ARBs versus various calcium channel blockers. However, none of these

clinical trials included head-to-head comparisons of valsartan to any of the other ARBs. For example, the "ARB Flashcard" includes the statements that valsartan 80 mg had comparable efficacy to amlodipine 5 mg, but that irbesartan 75 mg to 150 mg was **less effective** than amlodipine 5 mg or 5 mg to 10 mg. These statements imply that valsartan is superior to irbesartan. However, data comparing valsartan or irbesartan to amlodipine do not support claims comparing valsartan to irbesartan. Therefore, the implication that Diovan has superior efficacy is false or misleading because it is not supported by substantial evidence.

4. **Patient Brochure (Medication switch)**

In this "Medication Switch" patient brochure, you present the statement: "Information on why your medication that looked like this (Cozaar[1]), has been changed to this (Diovan)." Following this statement, a question and answer format is presented addressing "Some commonly asked questions about Diovan." For example:

Q. There are many different blood pressure medications. Why did my doctor choose DIOVAN?

A. DIOVAN not only lowers blood pressure effectively, but clinical studies have shown that DIOVAN seldom causes uncomfortable side effects.

This presentation implies that the patient's medication was switched from Cozaar to Diovan because Diovan possesses a superior tolerability profile. Claims that Diovan is safer or more tolerable than other therapies are false or misleading in the absence of adequate and well-controlled comparative trials demonstrating the claimed superior tolerability.

Lacking in fair balance

Promotional materials are false or misleading if they contain a representation or suggestion that a drug is safer, has less incidence, or has less serious side effects than has been demonstrated by substantial evidence. DDMAC has reviewed the "Medication Switch" patient brochure and the "Starter program" physician/patient brochure and has determined that they are misleading because you have failed to adequately disclose important risk information associated with the use of Diovan.

The boxed warning in the approved product labeling for Diovan states:

> **When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the**

1. Cozaar (losartan potassium) is a product of Merck & Co., Inc.

developing fetus. When pregnancy is detected, Diovan should be discontinued as soon as possible.

Notwithstanding this boxed warning, in the "Medication Switch" patient brochure, for example, a piece directed to patients, you present the following information concerning the risk of Diovan therapy during pregnancy:

Q. Should I continue taking DIOVAN if I'm pregnant?

A. Please contact your physician immediately. Your doctor will probably discontinue Diovan therapy because of concerns about its possible effect on the unborn child.

This presentation is inadequate to communicate the serious risk of fetal injury or death if Diovan is used during the second and third trimesters of pregnancy, as described in the boxed warning contained in its approved labeling. Therefore, the "Medication Switch" patient brochure and the "Starter program" physician/patient brochure are misleading because they minimize the risks associated with Diovan therapy, implying that it is safer than demonstrated by substantial evidence.

Additionally, based on the statement in the "Starter Program" physician/patient brochure and the "ARB flashcard" to "See Warnings in complete Prescribing Information (PI) available from sales representative," it appears that these pieces are not being disseminated to physicians with the PI. Dissemination of promotional labeling pieces without the information contained in the PI is in violation of the Act and its implementing regulations, and would further hinder access to information concerning the risks of Diovan therapy.

Finally, promotional materials must present information relating to contraindications, warnings, precautions, and side effects with a prominence and readability reasonably comparable to the presentation of information relating to the effectiveness of the drug. DDMAC has reviewed the "ARB flashcard" and "Starter program" physician/patient brochure and has determined that they are misleading because the risk information associated with the use of Diovan is not presented in a reasonably comparable manner to presentation of efficacy claims.

For example, on the front of the physician section of the "Starter Program" physician/patient brochure, claims for the efficacy of Diovan are presented in large, bold, colorful letters. However, the risk information is presented in small sized print, as a footnote, at the bottom of the page. This presentation is misleading because the risk information is not presented in a reasonably comparable manner.

Novartis should immediately cease distribution of these and other similar promotional materials for Diovan that contain the same or similar claims or presentations. DDMAC notes that other

promotional materials for Diovan contain similar presentations of other on-going investigations besides the Val-HeFT trial, that imply that Diovan is useful for conditions or purposes that are not approved or supported by substantial evidence. These materials should also be discontinued immediately.

Novartis should submit a written response to DDMAC on or before October 7, 1999, describing its intent and plans to comply with the above. In its letter to DDMAC, Novartis should include a list of materials discontinued and the date on which these materials were discontinued.

Novartis 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 Novartis that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #7893 in addition to the NDA number.

Sincerely,

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