DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Paulo Costa
President and Chief Executive Officer
Novartis Pharmaceuticals Corporation
One Health Plaza
Building 701, Suite 750
East Hanover, NJ 07936

RE: NDA # 21-283
Diovan® (valsartan) Tablets
MACMIS ID # 12379

WARNING LETTER

Dear Mr. Costa:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a professional sales aid (DIO-1176) (the sales aid) for Diovan® (valsartan) Tablets, submitted by Novartis Pharmaceuticals Corporation (Novartis) under cover of Form FDA 2253. The sales aid claims that Diovan is effective in treating patients with type 2 diabetes and hypertension to preserve renal function, a claimed use that is not approved and that has not, to our knowledge, been demonstrated by substantial evidence or substantial clinical experience. The sales aid is, therefore, false or misleading in violation of the Federal Food, Drug, and Cosmetic Act (Act). 21 U.S.C. § 352(a). Cf. 21 CFR 202.1(e)(6)(i). The sales aid, like other promotional materials Novartis has disseminated in the past, encourages use of Diovan in conditions for which FDA has not reviewed safety and effectiveness data, instead of other therapies that have demonstrated safety and effectiveness in these conditions.

Background

Diovan is an angiotensin receptor blocker or ARB. It is indicated for the treatment of (1) hypertension and (2) heart failure (NYHA class II-IV) in patients who are intolerant of angiotensin-converting enzyme inhibitors.

Diovan has not been shown to be effective in the treatment of any condition related to diabetes. Specifically, to our knowledge, Diovan has not been shown to be effective in preserving renal function in diabetics. In contrast, there are two ARBs (losartan, irbesartan) that have demonstrated effectiveness in the treatment of patients with diabetic nephropathy, decreased

renal function (elevated serum creatinine) and proteinuria in patients with type 2 diabetes and hypertension. In this population, losartan and irbesartan have been shown to reduce the rate of loss of renal function as measured by the occurrence of doubling of serum creatinine or end stage renal disease (ESRD) (need for dialysis or kidney transplantation).

We have previously communicated with you regarding promotion of Diovan for uses for which FDA has not reviewed safety and effectiveness data. On September 23, 1999, DDMAC sent Novartis an untitled letter regarding the promotion of Diovan Capsules for left ventricular hypertrophy and congestive heart failure. In that letter, we requested that you discontinue disseminating promotional materials containing unsubstantiated effectiveness claims for the drug. As described in DDMAC's letter to Novartis dated November 4, 1999, DDMAC subsequently identified a promotional piece titled "Diovan Phase III/IV Clinical Brochure" (DIO-8048-A) that had not been discontinued by Novartis as we had requested. Our November 4 letter stated: "Similar to the violations cited in our September 23, 1999 letter, this brochure creates the same unsubstantiated impression of anticipated efficacy for use of Diovan for congestive heart failure and other conditions, including . . . delaying or preventing diabetic nephropathy; cardiovascular disease, including CVD-related death, and diabetic retinopathy in patients with type 2 diabetes" (emphasis added). In a letter to DDMAC dated November 18, 1999, Novartis agreed to discontinue use of this brochure. More recently, DDMAC identified the sales aid, which claims that Diovan is effective in diabetes.

False or Misleading Promotion

The sales aid, entitled "NEW MARVAL STUDY: In patients with type 2 diabetes and uncontrolled BP > 130/80 mm Hg," includes the following statements:

- Diovan Reduced Urine Albumin Excretion by 44% ($P<0.05$)
- Diovan demonstrated a progressive lowering effect of UAER
- 30% of patients treated with Diovan returned to normoalbuminuria (<20 μg/min) by week 24
- NEW: ADA Recommends Use of ARBs First-Line for Hypertensive Patients with Type 2 Diabetes
- 75% of diabetes complications linked to high blood pressure
- Diabetes and hypertension are the two leading causes of ESRD

The sales aid thus claims that, by reducing urine albumin excretion, progressively lowering UAER, and returning patients to normal albumin levels, Diovan delays the progression to ESRD in type 2 diabetic patients with hypertension. Although albuminuria signals the presence of diabetic nephropathy, FDA is not aware of substantial evidence or substantial clinical experience demonstrating that reducing urine albumin excretion, progressively lowering UAER, or returning patients to normal albumin levels will delay progression to ESRD. The MARVAL study, cited in the sales aid to support the above statements, does not constitute substantial evidence or substantial clinical experience in support of the claim, because the study does not show any clinical benefit in diabetic nephropathy or ESRD. It shows, at most, effects on a biomarker that has not been shown to correlate with a change in progression to ESRD.

Conclusion and Requested Actions

We are not aware of substantial evidence or substantial clinical experience demonstrating that Diovan is useful in patients with type 2 diabetes and hypertension to delay progression to ESRD, as claimed in your sales aid. As discussed above, the study on which you rely is not adequate to substantiate this claim. Accordingly, your sales aid is false or misleading in violation of the Act, 21 U.S.C. § 352(a). Cf. 21 CFR 202.1(e)(6)(i).

Because of the significant public health and safety concerns raised by your sales aid, we request that you immediately cease the dissemination of promotional materials for Diovan that contain claims the same as or similar to those described above and provide a plan of action to disseminate accurate and complete information to the audience(s) that received the violative promotional materials. Please submit a written response to this letter on or before May 5, 2004, describing your intent to comply with this request, listing all promotional materials for Diovan that contain claims the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, Maryland 20857, facsimile at 301-594-6771. In all future correspondence regarding this matter, please refer to MACMIS ID # 12379 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Diovan comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violation discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

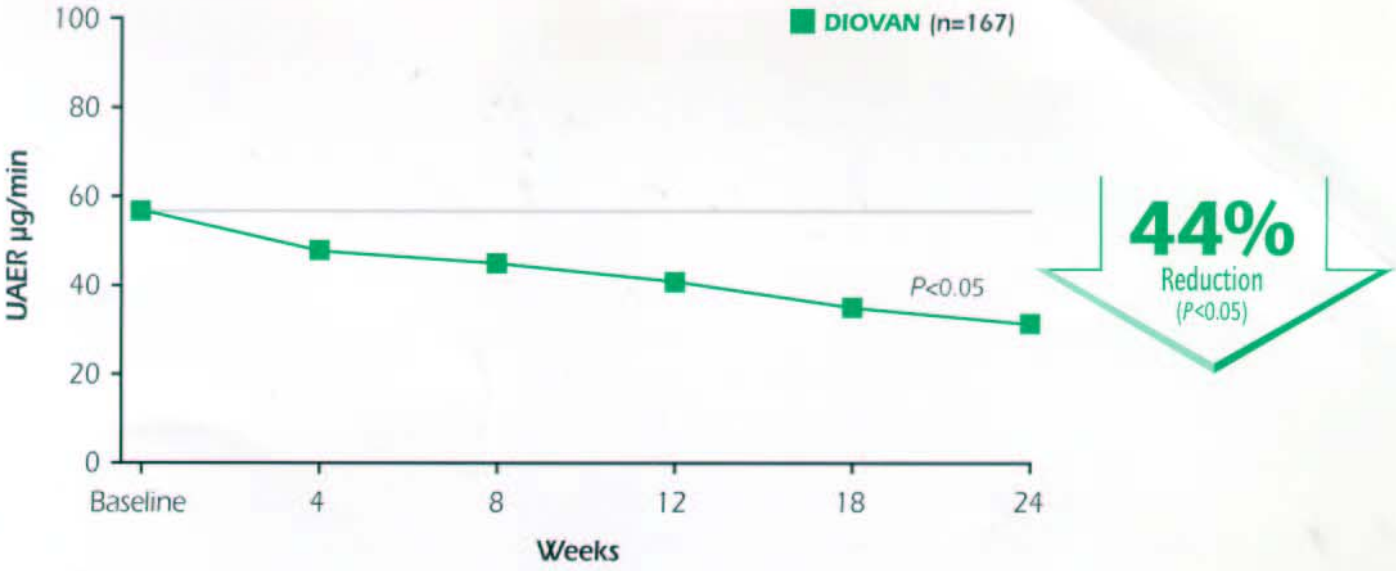
Thomas W. Abrams, RPh, MBA
Director
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Abrams
4/21/04 04:21:51 PM

DIOVAN Reduced Urine Albumin Excretion by 44% ($P<0.05$)



167 patients with microalbuminuria, type 2 diabetes, and mean BP of 147/85 mm Hg at baseline

- DIOVAN demonstrated a progressive lowering effect of UAER
- 30% of patients treated with DIOVAN returned to normoalbuminuria (<20 µg/min) by week 24

USE IN PREGNANCY: 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 developing fetus. When pregnancy is detected, DIOVAN should be discontinued as soon as possible. See **WARNINGS** in complete Prescribing Information provided separately.

No significant differences between adverse events (AEs), DIOVAN vs placebo. AEs more frequent than placebo: viral infection (3% vs 2%), fatigue (2% vs 1%), abdominal pain (2% vs 1%); the most common AEs: headache and dizziness. An increase in dizziness was observed with 320 mg (8%) vs 10 mg to 160 mg (2% vs 4%).

Care should be exercised with dosing of DIOVAN in patients with severe renal impairment. As a consequence of inhibiting the renin-angiotensin system, changes in renal function may be observed in susceptible individuals (eg, patients with renal artery stenosis and severe congestive heart failure).

In patients with more severe renal impairment, creatinine clearance is <30mL/min, DIOVAN HCT is not recommended.

Diovan®
valsartan tablets

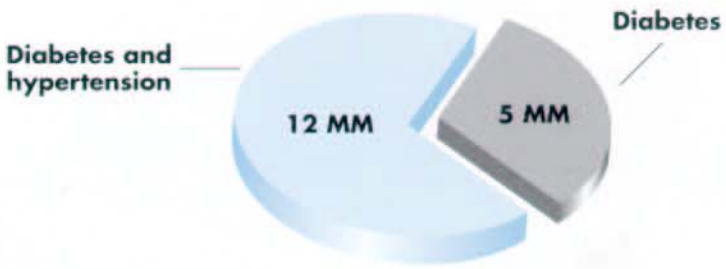
NEW: ADA Recommends Use of ARBs First-line for Hypertensive Patients With Type 2 Diabetes

Tighter BP control required

ADA and NKF recommend lower BP goals in diabetes[2,3]	
Goal BP **<130/80** mm Hg (no proteinuria)	Goal BP **<125/75** mm Hg (proteinuria >1g/day)

73% of patients with diabetes have BP ≥130/80 mm Hg[4]

Prevalence of diabetes and coexisting hypertension in the US



FACT: 75% of diabetes complications linked to high blood pressure[5]

Diabetes and hypertension are the two leading causes of ESRD

Primary diagnosis for patients who start Dialysis