DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Graydon Elliott, Director
Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936

RE: NDA# 21-990
Exforge (amlodipine and valsartan) Tablets
MACMIS #18874

Dear Mr. Elliott:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed "The BP Goal Money-Back Guarantee" brochure (EXR20016) (brochure) for Exforge (amlodipine and valsartan) Tablets (Exforge), submitted by Novartis Pharmaceuticals Corporation (Novartis) under cover of Form FDA-2253. The brochure is false or misleading because it overstates the efficacy of the drug, presents unsubstantiated superiority claims and omits serious risks associated with the drug. Thus, the brochure misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a) & 321(n). *Cf.* 21 CFR 202.1(e)(6)(i). In addition, it appears that the brochure was accompanied by an outdated version of the FDA-approved product labeling (PI) for Exforge, in violation of 21 CFR 201.100(d).

Background

The INDICATIONS and USAGE section of the PI[1] for Exforge states (in pertinent part):

> Exforge (amlodipine and valsartan) is indicated for the treatment of hypertension.
> Exforge may be used in patients whose blood pressure is not adequately controlled on either monotherapy.
> Exforge may also be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.
> The choice of Exforge as initial therapy for hypertension should be based on an assessment of potential benefits and risks including whether the patient is likely to tolerate the lowest dose of Exforge.

In addition, the INDICATIONS AND USAGE section of the PI states:

[1] The PI submitted with the promotional piece on Form FDA-2253 was dated April 2007. However, the brochure was submitted on February 17, 2009, with a listed dissemination date of February 24, 2009; the most current version of the FDA-approved PI as of these dates was the July 23, 2008 version, and that is the version referred to in this letter. Although not relevant to the issues in this letter, we note that the PI for Exforge was again updated on March, 30, 2010.

Data from the high-dose multifactorial study [*see Clinical Studies (14)*] provide estimates of the probability of reaching a blood pressure goal with Exforge compared to amlodipine or valsartan monotherapy. The figures below provide estimates of the likelihood of achieving systolic or diastolic blood pressure control with Exforge 10/320 mg, based upon baseline systolic or diastolic blood pressure. The curve of each treatment group was estimated by logistic regression modeling. The estimated likelihood at the right tail of each curve is less reliable due to small numbers of subjects with high baseline blood pressures.

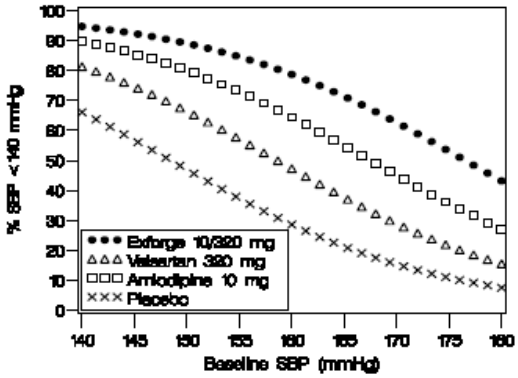

Figure 1: Probability of Achieving Systolic Blood Pressure <140 mmHg at Week 8

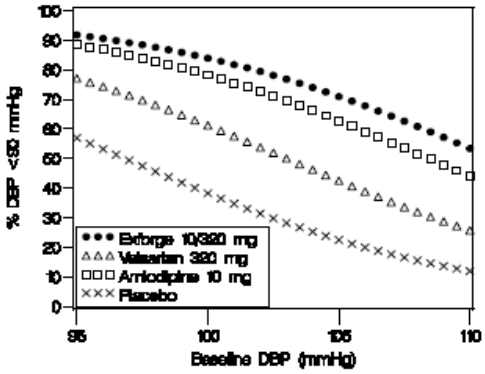

Figure 2: Probability of Achieving Diastolic Blood Pressure <90 mmHg at Week 8

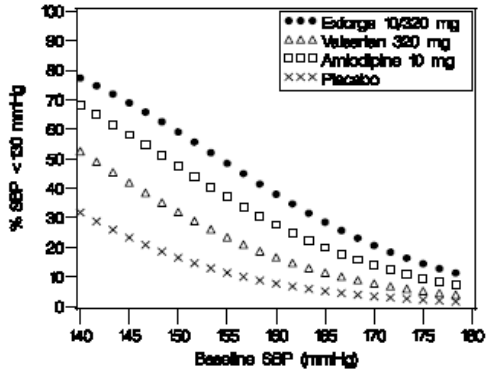

Figure 3: Probability of Achieving Systolic Blood Pressure <130 mmHg at Week 8

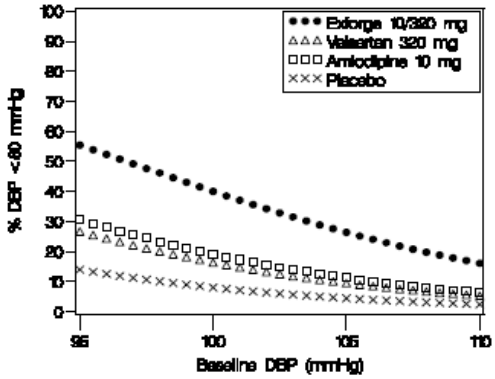

Figure 4: Probability of Achieving Diastolic Blood Pressure <80 mmHg at Week 8

For example, a patient with a baseline blood pressure of 160/100 mmHg has about a 67% likelihood of achieving a goal of <140 mmHg (systolic) and 80% likelihood of achieving <90 mmHg (diastolic) on amlodipine alone, and the likelihood of achieving these goals on valsartan alone is about 47% (systolic) or 62% (diastolic). The likelihood of achieving these goals on Exforge rises to about 80% (systolic) or 85% (diastolic). The likelihood of achieving these goals on placebo is about 28% (systolic) or 37% (diastolic).

Exforge is associated with a number of serious risks. The PI for Exforge includes a boxed warning which states (emphasis in original):

> **WARNING: AVOID USE IN PREGNANCY**
>
> **When pregnancy is detected, discontinue Exforge® as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus**. . . .

Additional Warnings and Precautions associated with Exforge include the risk of hypotension, risks of myocardial infarction or increased angina, impaired hepatic functions, impaired renal function, and congestive heart failure.

The DRUG INTERACTIONS section of the PI states, ". . . concomitant use of potassium sparing diuretics (e.g., spironolactone, triamterine, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine."

The most common adverse reactions in clinical trials associated with Exforge were peripheral edema, nasopharyngitis, upper respiratory tract infection, and dizziness.

The CLINICAL STUDIES section of the PI indicates that Exforge was studied in 2 placebo-controlled and 4 active-controlled trials in hypertensive patients. At week 8, the two-placebo controlled trials and the two active-controlled trials that evaluated patients not adequately controlled on valsartan 160 mg or amlodipine 10 mg found "the combination treatment [to be] . . . significantly superior to the monotherapy component in reduction of diastolic and systolic blood pressures." Two active-controlled clinical trials evaluated patients with mild to moderate hypertension not adequately controlled on valsartan 160 mg or amlodipine 10 mg. In the active-controlled trial conducted in patients who were not adequately controlled on valsartan 160 mg, the treatment difference for Exforge 10/160 mg versus valsartan 160 mg in diastolic and systolic blood pressures was 4.8 and 5.7mmHg, respectively. In the active-controlled trial conducted in patients who were not adequately controlled on amlodipine 10 mg, the treatment difference for Exforge 10/160 mg versus amlodipine 10 mg in diastolic and systolic blood pressures was 1.8 and 1.9 mmHg, respectively.

The other two active-controlled clinical trials evaluated Exforge as initial therapy in patients with moderate to severe hypertension where the patients were randomized to receive either Exforge or amlodipine monotherapy. At the primary endpoint of 8 weeks for one trial, the treatment difference for Exforge versus amlodipine in diastolic and systolic blood pressures was 6.7 and 2.8 mmHg, respectively. At the primary endpoint of 4 weeks for the other trial, the treatment difference for Exforge versus amlodipine in diastolic and systolic blood pressures was 6.6 and 3.9 mmHg, respectively.

Overstatement of Efficacy/Unsubstantiated Superiority Presentation

Promotional materials are misleading if they represent or suggest that a drug is more effective than has been demonstrated by substantial evidence or substantial clinical

experience. The brochure presents the following claims (underlined emphasis added; footnote omitted):

- "*The* BP GOAL MONEY-BACK
  Guarantee

  Getting to goal is one of the most important things you can do when it comes to your blood pressure. That's why EXFORGE guarantees you'll reach the goal set by your doctor—or your money back."

- "**What is the BP Goal Money-Back Guarantee?**
  Your doctor will set your target blood pressure before you begin taking EXFORGE (amlodipine and valsartan) tablets. If you have not reached that goal after being on the highest dose of EXFORGE (10/320 mg) <u>for at least 30 days</u> . . . ."

The above presentation significantly misrepresents what is known about the efficacy of Exforge. Specifically, the "guarantee" claims overstate the effect Exforge will have on lowering a patient's blood pressure and reaching a patient's blood pressure (BP) goal. According to the CLINICAL STUDIES section of Exforge's PI (see Background section), the treatment difference for Exforge 10/160 mg versus valsartan 160 mg in diastolic and systolic blood pressures was 4.8 and 5.7mmHg, respectively. The treatment difference for Exforge 10/160 mg versus amlodipine 10 mg in diastolic and systolic blood pressures was 1.8 and 1.9 mmHg, respectively. Furthermore, in the two active-controlled trials conducted in which Exforge was administered as initial therapy, the treatment difference between Exforge versus amlodipine in diastolic and systolic blood pressures was 6.7 and 2.8 mmHg, respectively, in one trial, and 6.6 and 3.9 mmHg, respectively, in the other trial. We note that the INDICATION AND USAGE section of the PI presents estimates of the **likelihood** of achieving systolic or diastolic blood pressure control with Exforge 10/320 mg, based on baseline systolic or diastolic blood pressure. We also note that according to the PI, a patient with a baseline blood pressure of 160/100 mmHg has about 80% (systolic) or 85% (diastolic) likelihood of achieving a goal of <140/90 mmHg. However, as seen in Figures 1- 4 (see Background section), as the baseline diastolic and systolic blood pressures increase, the probability of achieving systolic or diastolic blood pressure goals **decreases**. Therefore, while Exforge has been shown to lower blood pressure, the clinical trials do not support the claims "guarantee[ing] you'll reach the goal," regardless of a patient's baseline blood pressure.

The "guarantee" claims also misleadingly suggest that Exforge is more effective than other antihypertensives and that it **will** lower blood pressure to the goal blood pressure level within at least 30 days, when this has not been demonstrated by substantial evidence or substantial clinical experience. We note that the CLINICAL STUDIES section of the PI for Exforge includes information that Exforge is superior to its individual components; however, we are not aware of any adequate and well-controlled head-to-head studies supporting the implication that Exforge is more effective than other individual treatments or combination treatments for hypertension and that Exforge **will** lower blood pressure to the goal blood

pressure level within at least 30 days. If, in fact, you do have data to support these implications, please submit them to FDA for review.

Omission of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. While the brochure includes information from the Boxed Warning, some Warnings and Precautions, and Adverse Reactions associated with Exforge, it fails to include other important and serious risk information. Specifically, the brochure fails to reveal Warnings and Precautions regarding hepatic impairment and interactions with potassium sparing diuretics, potassium supplements, or salt substitutes containing potassium.

Use of Outdated Product Labeling

It appears that the promotional brochure was disseminated with an outdated version of the PI, in violation of 21 CFR 201.100(d). The PI submitted with the promotional piece on Form FDA-2253 was dated April 2007. However, the listed dissemination date of the brochure was February 24, 2009; the most current version of the FDA-approved PI as of February 24, 2009 was the July 23, 2008 version, not the April 2007 version.

Conclusion and Requested Action

For the reasons discussed above, the brochure misbrands Exforge in violation of the Act, 21 U.S.C. 352(a) & 321(n). 21 CFR 201.100(d); *cf*. 21 CFR 202.1(e)(6)(i).

DDMAC requests that Novartis immediately cease the dissemination of violative promotional materials for Exforge, such as those described above. Please submit a written response to this letter on or before August 13, 2010, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Exforge that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. If you have any questions or comments, please contact me by facsimile at (301) 847-8444, or write to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705. In all future correspondence regarding this matter, please refer to MACMIS ID # 18874 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 Exforge comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Zarna Patel, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communication

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21990	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	EXFORGE(AMLODIPINE BESYLATE & VALSARTAN

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

/s/

ZARNA PATEL
07/30/2010