



NDA 20-818/S-035

Novartis Pharmaceuticals Corporation
Attention: Ms. Nancy A. Price
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Price:

Please refer to your supplemental new drug application dated November 13, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Diovan HCT (valsartan/hydrochlorothiazide) 80/12.5 mg, 160/12.5 mg, 160/25, 320/12.5, and 320/25 mg Tablets.

This “Changes Being Effected” supplemental new drug application provides for revisions to the **boxed “USE IN PREGNANCY” warning, WARNINGS/ Fetal/Neonatal Morbidity and Mortality** subsection, and the **Information for Patients/Pregnancy** subsection to update the pregnancy information based on a publication regarding the use of ACE inhibitors during the first trimester of pregnancy. This supplemental new drug application provides for electronic final printed labeling revised as follows:

1. Under the **boxed “USE IN PREGNANCY” warning**, the first sentence was changed from:

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.

To:

When used in pregnancy, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus.

2. Under the **WARNINGS/Fetal/Neonatal Morbidity and Mortality** subsection the third paragraph was changed from:

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should advise the patient to discontinue the use of valsartan as soon as possible.

To:

In addition, first trimester use of ACE inhibitors, a specific class of drugs acting on the renin-angiotensin system, has been associated with a potential risk of birth defects in retrospective data. Healthcare professionals that prescribe drugs acting directly on the renin-angiotensin system should counsel women of childbearing potential about the potential risks of these agents during pregnancy.

3. Under the **Information for Patients/Pregnancy** subsection the paragraph has been changed from:

Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be

told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

To:

Female patients of childbearing age should be told about the consequences of exposure to drugs that act on the renin-angiotensin system. Discuss other treatment options with female patients planning to become pregnant. Patients should be asked to report pregnancies to their physicians as soon as possible.

In addition, the following minor editorial changes were noted:

At the end of the package insert, the issue date has been updated from “REV: MARCH 2006” to “REV: OCTOBER2006 and the statement “Printed in U.S.A.” has been added.

We have completed our review of this supplemental new drug application and it is approved, effective on the date of this letter, for use as recommended in the electronic labeling submitted on November 13, 2006.

At the time of your next printing, please make the following minor editorial correction:

Under the “**WARNINGS/Fetal/Neonatal Morbidity and Mortality**” subsection, delete the word “inadvertently” from the third sentence of the first paragraph so that it reads:

There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction when pregnant women have taken valsartan.

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D.
Regulatory Health Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Norman Stockbridge
9/6/2007 05:18:09 PM