

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-283/S-021

Trade Name: Diovan 40, 80, 160, and 320 mg Tablets

Generic Name: valsartan

Sponsor: Novartis Pharmaceuticals Corporation

Approval Date: August 17, 2007

Purpose: 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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-283/S-021

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-283/S-021

APPROVAL LETTER



NDA 21-283/S-021

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 (valsartan) 40, 80, 160, and 320 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 change was noted:

At the end of the package insert, the issue date has been updated from “REV: MARCH 2006” to “REV: OCTOBER2006.”

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.

We note that in the Structured Product Labeling (SPL) version of this submission, under the “**CLINICAL PHARMACOLOGY/Pharmacodynamics and Clinical Effects/Post-Myocardial Infarction**” subsection, the title “**Effects on Mortality Amongst Subgroups in VALIANT**” is missing from the last table. Please re-add this title to the table in future SPL versions you submit.

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
8/17/2007 02:47:28 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-283/S-021

OTHER REVIEW(S)

RHPM Review of Final Printed Labeling (FPL)

Application: NDA 21-283/S-021
Diovan (valsartan) Tablets
40, 80, 160, and 320 mg

Applicant: Novartis Pharmaceuticals Corporation

Document Date: November 13, 2006

Receipt Date: November 14, 2006

Background: 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 the following June 8, 2006 publication in *New England Journal of Medicine* regarding the use of ACE inhibitors during the first trimester of pregnancy:

- Cooper WO, Hernandez-Diaz S, Arbogast PG et al. Major Congenital Malformations after First-Trimester Exposure to ACE Inhibitors. *N Engl J Med* 2006; 354:2443-51.

Review: When compared with the last approved labeling (SLR-018; approved November 22, 2006), the following changes were noted:

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.

Dr. Targum stated in a 6/21/07 email that the above changes are acceptable.

Dr. Resnick stated on 6/28/07 that the above changes are acceptable.

In addition, the following minor editorial changes were also noted:

1. Under the “**CLINICAL PHARMACOLOGY/Pharmacodynamics and Clinical Effects/Post-Myocardial Infarction**” subsection, the title “**Effects on Mortality Amongst Subgroups in VALIANT**” is missing from the last table in the SPL version and should be re-added.
2. At the end of the package insert, the issue date has been updated from “REV: MARCH 2006” to “REV: OCTOBER2006.”

Note: The November 22, 2006 approval letter for SLR-018 stated that the following editorial correction should be made at the time of the next printing:

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.

As pending supplement SLR-021 was submitted prior to issuance of the approval letter for SLR-018, the above change was not included in the pending supplement and will be requested again in the approval letter for SLR-021.

There were no other changes than those listed when compared with the last approved labeling (SLR-018; approved November 22, 2006).

Comments/Recommendations: I will draft an approval (AP) letter for Dr. Stockbridge’s signature. The AP letter will state the following:

We note that in the Structured Product Labeling (SPL) version of this submission, under the “**CLINICAL PHARMACOLOGY/Pharmacodynamics and Clinical Effects/Post-Myocardial Infarction**” subsection, the title “**Effects on Mortality Amongst Subgroups in VALIANT**” is missing from the last table. Please re-add this title to the table in future SPL versions you submit.

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.

Quynh Nguyen, Pharm.D.
Regulatory Health Project Manager

QN/6-12-07/7-26-07/8-17-07

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

/s/

Quynh Nguyen
8/17/2007 01:30:22 PM
CSO

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-283/S-021

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



NDA 20-818/S-035
21-283/S-021

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

Dear Ms. Price:

We have received your supplemental drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

NDA 20-818 for Diovan HCT (valsartan/hydrochlorothiazide) 80/12.5, 160/12.5, 160/25,
320/12.5 and 320/25 mg Tablets

NDA 21-283 for Diovan (valsartan) 40, 80, 160 and 320 mg Tablets

Date of supplement: November 13, 2006

Date of receipt: November 14, 2006

These supplemental applications, submitted as "Supplement- Change Being Effected" proposes revisions to the package insert for Diovan and Diovan HCT Tablets.

Unless we notify you within 60 days of the receipt date that these applications are not sufficiently complete to permit a substantive review, we will file the applications on January 13, 2007 in accordance with 21 CFR 314.101(a).

Please cite the application numbers listed above at the top of the first page of all submissions to these applications. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 20-818/S-035

21-283/S-021

Page 2

If you have any questions, please contact:

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

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
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/

Edward Fromm

11/27/2006 08:17:28 AM