



NDA 021990/S-017
NDA 022314/S-012

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Nancy Price
Global Program Regulatory Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Ms Price:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received December 22, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Exforge (amlodipine/valsartan) 5/160 mg, 10/160 mg, 5/320 mg, and 10/320 mg Tablets (NDA 021990) and Exforge HCT (amlodipine/valsartan/hydrochlorothiazide) 5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg, and 10/320/25 mg Tablets (NDA 022314).

These “Prior Approval” supplemental new drug applications provide for labeling revised as follows:

The following changes were made for NDA 021990:

1. In **HIGHLIGHTS** and **Full Prescribing Information**, the boxed warning was changed:

<p style="text-align: center;">WARNING: FETAL TOXICITY</p> <ul style="list-style-type: none">• When pregnancy is detected, discontinue Exforge as soon as possible (5.1)• Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus (5.1)
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2. Under **WARNINGS AND PRECAUTIONS**, the section was changed from:

5.1 Fetal/Neonatal Morbidity and Mortality

Exforge can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Drugs that act on the renin angiotensin system can cause fetal and neonatal morbidity and mortality when used in pregnancy. In several dozen published cases, ACE inhibitor use during the second and third trimesters of pregnancy was associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death [*see Use in Specific Populations (8.1)*].

To:

5.1 Fetal toxicity Pregnancy Category D

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Exforge as soon as possible [*see Use in Specific Populations (8.1)*].

3. Under **USE IN SPECIFIC POPULATIONS**, the section was changed from:

8.1 Pregnancy

Pregnancy Category D [*see Warnings and Precautions (5.1)*]

Exforge, like other drugs that act on the renin angiotensin system, can cause fetal and neonatal morbidity and death when used during the second or third trimester of pregnancy. Exforge can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Angiotensin II receptor antagonists, like valsartan, and angiotensin converting enzyme (ACE) inhibitors exert similar effects on the renin-angiotensin system. In several dozen published cases, ACE inhibitor use during the second and third trimesters of pregnancy was associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios was also reported, presumably from decreased fetal renal function. In this setting, oligohydramnios was associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus were also reported, although it is not clear whether these occurrences were due to exposure to the drug. In a retrospective study, first trimester use of ACE inhibitors, a specific class of drugs acting on the renin angiotensin system, was associated with a potential risk of birth defects.

When pregnancy occurs in a patient using Exforge, the physician should discontinue Exforge treatment as soon as possible. The physician should inform the patient about potential risks to the fetus based on the time of gestational exposure to Exforge (first trimester only or later). If exposure occurs beyond the first trimester, an ultrasound examination should be done.

In rare cases when another antihypertensive agent cannot be used to treat the pregnant patient, serial ultrasound examinations should be performed to assess the intraamniotic environment. Routine fetal testing with non-stress tests, biophysical profiles, and/or contraction stress tests may be appropriate based on gestational age and standards of care in the community. If oligohydramnios occurs in these situations, individualized decisions about continuing or discontinuing Exforge treatment and about pregnancy management should be made by the patient, her physician, and experts in the management of high risk pregnancy. Patients and physicians should be aware that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to Exforge should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, these infants may require blood pressure and renal perfusion support. Exchange transfusion or dialysis may be required to reverse hypotension and/or support decreased renal function.

Healthcare professionals who prescribe drugs acting directly on the renin-angiotensin system should counsel women of childbearing potential about the risks of these agents during pregnancy [see Nonclinical Toxicology (13.2)].

To:

8.1 Pregnancy

Pregnancy Category D

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Exforge as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue Exforge, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to Exforge for hypotension, oliguria, and hyperkalemia [*see Use in Specific Populations (8.4)*]

4. Under **USE IN SPECIFIC POPULATIONS/Pediatric Use**, a new section was added:

Neonates with a history of in utero exposure to Exforge:

If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

5. Under **PATIENT COUNSELING INFORMATION**, the section was changed from:

Pregnancy: Female patients of childbearing age should be told that use of drugs like valsartan that act on the renin-angiotensin system can cause serious problems in the fetus and infant including: low blood pressure, poor development of skull bones, kidney failure and death. Discuss other treatment options with female patients planning to become pregnant. Women using Exforge who become pregnant should notify their physicians as soon as possible.

To:

Pregnancy: Female patients of childbearing age should be told about the consequences of exposure to Exforge during pregnancy. Discuss treatment options with women planning to become pregnant. Patients should be asked to report pregnancies to their physicians as soon as possible.

6. In the Patient Package Inert (PPI), Under **What is the most important information I should know about EXFORGE HCT?**, the text was revised from:

If you become pregnant while taking EXFORGE, stop taking EXFORGE HCT and call your doctor right away. EXFORGE can harm an unborn baby causing injury or death. Talk to your doctor about other treatment options to lower your blood pressure before taking EXFORGE if you plan to become pregnant.

To:

What is the most important information I should know about EXFORGE?

- EXFORGE can cause harm or death to an unborn baby.
- Talk to your doctor about other ways to lower your blood pressure if you plan to become pregnant.
- If you get pregnant while taking EXFORGE, tell your doctor right away.

The following changes were made for NDA 022314:

1. In **HIGHLIGHTS** and **Full Prescribing Information**, the boxed warning was changed:

WARNING: FETAL TOXICITY

- **When pregnancy is detected, discontinue Exforge HCT as soon as possible (5.1)**
- **Drugs that act directly on the rennin-angiotensin system can cause injury and death to the developing fetus (5.1)**

2. Under **WARNINGS AND PRECAUTIONS**, the section was changed from:

5.1 Fetal/Neonatal Morbidity and Mortality

Exforge HCT can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Drugs that act on the renin angiotensin system can cause fetal and neonatal morbidity and mortality when used in pregnancy. In several dozen published cases, ACE inhibitor use during the second and third trimesters of pregnancy was associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death [*see Use in Specific Populations (8.1)*].

To:

**5.1 Fetal toxicity
Pregnancy Category D**

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death.

When pregnancy is detected, discontinue Exforge HCT as soon as possible [*see Use in Specific Populations (8.1)*].

3. Under **USE IN SPECIFIC POPULATIONS**, the section was changed from:

8.1 Pregnancy

Valsartan, like other drugs that act on the renin-angiotensin system, can cause fetal and neonatal morbidity and death when used during the second or third trimester of pregnancy. If Exforge HCT is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Angiotensin II receptor antagonists, like valsartan, and angiotensin converting enzyme (ACE) inhibitors exert similar effects on the renin-angiotensin system. In several dozen published cases, ACE inhibitor use during the second and third trimesters of pregnancy was associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios was also reported, presumably from decreased fetal renal function. In this setting, oligohydramnios was associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus were also reported, although it is not clear whether these occurrences were due to exposure to the drug. In a retrospective study, first trimester use of ACE inhibitors, a specific class of drugs acting on the renin-angiotensin system, was associated with a potential risk of birth defects.

When pregnancy occurs in a patient using Exforge HCT, the physician should discontinue Exforge HCT treatment as soon as possible. The physician should inform the patient about potential risks to the fetus based on the time of gestational exposure to Exforge HCT (first trimester only or later). If exposure occurs beyond the first trimester, an ultrasound examination should be done.

In rare cases when another antihypertensive agent can not be used to treat the pregnant patient, serial ultrasound examinations should be performed to assess the intraamniotic environment. Routine fetal testing with non-stress tests, biophysical profiles, and/or contraction stress tests may be appropriate based on gestational age and standards of care in the community. If oligohydramnios occurs in these situations, individualized decisions about continuing or discontinuing Exforge HCT treatment and about pregnancy management should be made by the patient, her physician, and experts in the management of high risk pregnancy. Patients and physicians should be aware that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to Exforge HCT should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, these

infants may require blood pressure and renal perfusion support. Exchange transfusion or dialysis may be required to reverse hypotension and/or support decreased renal function.

Healthcare professionals who prescribe drugs acting directly on the renin-angiotensin system should counsel women of childbearing potential about the risks of these agents during pregnancy [see *Nonclinical Toxicology* (13.3)].

To:

8.1 Pregnancy

Pregnancy Category D

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Exforge HCT as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue Exforge HCT, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to Exforge HCT for hypotension, oliguria, and hyperkalemia [see *Use in Specific Populations* (8.4)]

4. Under **USE IN SPECIFIC POPULATIONS/Pediatric Use**, a new section was added:

Neonates with a history of in utero exposure to Exforge HCT:

If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

5. Under **PATIENT COUNSELING INFORMATION**, the section was changed from:

Pregnancy: Female patients of childbearing age should be told that use of drugs like Exforge HCT that act on the renin-angiotensin system can cause serious problems in the fetus and infant including: low blood pressure, poor development of skull bones, kidney failure and death. Discuss other treatment options with female patients planning to become pregnant. Women using Exforge HCT who become pregnant should notify their physicians as soon as possible.

To:

Pregnancy: Female patients of childbearing age should be told about the consequences of exposure to Exforge HCT during pregnancy. Discuss treatment options with women planning to become pregnant. Patients should be asked to report pregnancies to their physicians as soon as possible.

7. In the Patient Package Inert (PPI), Under **What is the most important information I should know about EXFORGE HCT HCT?**, the text was revised from:

If you become pregnant while taking EXFORGE HCT, stop taking EXFORGE HCT HCT and call your doctor right away. EXFORGE HCT can harm an unborn baby causing injury or death. Talk to your doctor about other treatment options to lower your blood pressure before taking EXFORGE HCT if you plan to become pregnant.

To:

What is the most important information I should know about EXFORGE HCT?

- EXFORGE HCT can cause harm or death to an unborn baby.
- Talk to your doctor about other ways to lower your blood pressure if you plan to become pregnant.
- If you get pregnant while taking EXFORGE HCT, tell your doctor right away.

We have completed our review of these supplemental applications, and they are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the

addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call:

Lori Anne Wachter, RN, BSN
Regulatory Project Manager for Safety
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, Pharm.D.
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

MARY R SOUTHWORTH
01/18/2012