DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022107/S-019

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Lily Chan, PharmD
Director
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Chan:

Please refer to your Supplemental New Drug Application (sNDA) dated and received December 22, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tekturna HCT (aliskiren/hydrochlorothiazide) 150/12.5 mg, 150/25 mg, 300/12.5 mg, and 300/25 mg Tablets.

This "Prior Approval" supplemental new drug application provides for labeling revised as follows:

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

> **WARNING: FETAL TOXICITY**
> - **When pregnancy is detected, discontinue Tekturna HCT 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)**

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

5.1 Fetal/Neonatal Morbidity and Mortality

Tekturna 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 directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*. In several dozen published cases, ACE inhibitors 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. In addition, first trimester use of ACE inhibitors has been associated with birth defects. Thiazides cross the placenta, and use of thiazides during pregnancy is associated with a risk of fetal

or neonatal jaundice, thrombocytopenia, and possible other adverse reactions that have occurred in adults.

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 Tekturna HCT as soon as possible. *[see Use in Specific Populations (8.1)]*

Thiazides cross the placenta, and use of thiazides during pregnancy is associated with a risk of fetal or neonatal jaundice, thrombocytopenia, and possible other adverse reactions that have occured in Tekturna HCT.

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

8.1 Pregnancy

Pregnancy Categories D *[See Warnings and Precautions (5.1)]*.

Tekturna HCT contains both aliskiren (a direct renin inhibitor) and hydrochlorothiazide (a thiazide diuretic). When administered during the second or third trimester of pregnancy, drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death.

Thiazides can cross the placenta, and use of thiazides during pregnancy is associated with a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults. Tekturna 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, apprise the patient of the potential hazard to the fetus.

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 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.

When pregnancy occurs in a patient using Tekturna HCT, the physician should discontinue Tekturna 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 Tekturna 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 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 Tekturna 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 Tekturna 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.

No reproductive toxicity studies have been conducted with the combination of aliskiren and hydrochlorothiazide. However, these studies have been conducted for aliskiren as well as hydrochlorothiazide alone.

Reproductive toxicity studies of aliskiren hemifumarate did not reveal any evidence of teratogenicity at oral doses up to 600 mg aliskiren/kg/day (20 times the maximum recommended human dose [MRHD] of 300 mg/day on a mg/m^2 basis) in pregnant rats or up to 100 mg aliskiren/kg/day (seven times the MRHD on a mg/m^2 basis) in pregnant rabbits. Fetal birth weight was adversely affected in rabbits at 50 mg/kg/day (3.2 times the MRHD on a mg/m^2 basis). Aliskiren was present in placenta, amniotic fluid and fetuses of pregnant rabbits.

When pregnant mice and rats were given hydrochlorothiazide at doses up to 3000 and 1000 mg/kg/day, respectively (about 600 and 400 times the MRHD) during their respective periods of major organogenesis, there was no evidence of fetal harm.

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 Tekturna 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 Tekturna 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 Tekturna HCT for hypotension, oliguria, and hyperkalemia. *[see Use in Specific Populations (8.4)]*
Thiazides cross the placenta, and use of thiazides during pregnancy is associated with a risk of fetal or neonatal jaundice, thrombocytopenia, and possible other adverse reactions that have occured in adults.

Reproductive toxicity studies of aliskiren hemifumarate did not reveal any evidence of teratogenicity at oral doses up to 600 mg aliskiren/kg/day (20 times the maximum recommended human dose [MRHD] of 300 mg/day on a mg/m^2 basis) in pregnant rats or up to 100 mg aliskiren/kg/day (seven times the MRHD on a mg/m^2 basis) in pregnant rabbits. Fetal birth weight was adversely affected in rabbits at 50 mg/kg/day (3.2 times the MRHD on a mg/m^2 basis). Aliskiren was present in placenta, amniotic fluid and fetuses of pregnant rabbits.

When pregnant mice and rats were given hydrochlorothiazide at doses up to 3000 and 1000 mg/kg/day, respectively (about 600 and 400 times the MRHD) during their respective periods of major organogenesis, there was no evidence of fetal harm.

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

   Neonates with a history of in utero exposure to Tekturna 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:

   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. 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 Tekturna 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.

6. The revision date and version number were updated.

There are no other changes from the last approved package insert.

The following change was made to the Patient Information Section:

1. Under **What is the most important information I should know about Tekturna HCT?**, the section was changed from:

IMPORTANT WARNING: Tekturna HCT may harm an unborn baby, causing injury and even death. If you get pregnant, stop taking Tekturna HCT and call your doctor right away. If you plan to become pregnant, talk to your doctor about other medicines to treat your high blood pressure before taking Tekturna HCT.

To:

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

Tekturna 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 Tekturna HCT, tell your doctor right away.

2. Under **Tell your doctor about all your medical conditions, including whether you:**, the firt bullet was changed from:

- are pregnant or planning to become pregnant. See IMPORTANT WARNING

To:

- are pregnant or planning to become pregnant. See What is the most important information I should know about Tekturna HCT?

3. Under Tekturna may cause serious side effects:, the first bullet was changed from:

- **Injury or death to an unborn baby.** See IMPORTANT WARNING

To:

- **Injury or death to an unborn baby.** See What is the most important information I should know about Tekturna HCT?

4. The revision date and version number were updated.

We have completed our review of this supplemental application, and it is 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
02/02/2012