DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 022107 / S-014

**SUPPLEMENT APPROVAL**

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

Dear Dr. Chan:

Please refer to your Supplemental New Drug Application (sNDA) dated April 13, 2011, received April 13, 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, 300/12.5 mg, 150/25 mg and 300/25 mg Tablets.

This "Prior Approval" supplemental new drug application provides for the following content changes, additional minor editorial changes were made, see attached labeling:

In **HIGHLIGHTS OF PRESCRIBING INFORMATION**

The trade name has been changed to all capital letters in the Highlights Limitation Statement.

The dosage form and route of administration description has been changed from, "Tablets, Oral" to "tablets, for oral use".

Under **HL, INDICATIONS AND USAGE**

The pharmacologic class has been changed from "direct renin inhibitor" to "renin inhibitor"

The indication has been changed to add,

> Tekturna HCT is a combination of aliskiren, a renin inhibitor, and hydrochlorothiazide (HCTZ), a thiazide diuretic, indicated for the treatment of hypertension, to lower blood pressure:
> - In patients not adequately controlled with monotherapy
> - As initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals (1)
>
> Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarction.

In **FULL PRESCRIBING INFORMATION: CONTENTS**

Reference to Section 6.2 Clinical laboratory findings has been deleted and Post-marketing Experience has been re-numbered to 6.2.

In **FULL PRESCRIBING INFORMATION**, the following have been added or ~~deleted~~;

Under **INDICATIONS AND USAGE**,

Tekturna HCT is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including hydrochlorothiazide. There are no controlled trials demonstrating risk reduction with Tekturna HCT.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

Under **ADVERSE REACTIONS**,

Section 6.2, **Clinical Laboratory Findings** was removed as an enumerated subsection, it remains a bolded heading. Section 6.3, **Post-marketing Experience** was renumbered to Section 6.2.

Under **DESCRIPTION,**

Tekturna HCT is a fixed combination of aliskiren, an orally active, nonpeptide, direct renin inhibitor, and hydrochlorothiazide, a thiazide diuretic that is provided as tablets for oral administration.

Under **CLINICAL STUDIES,**

***Amlodipine***
Aliskiren 150 mg and 300 mg and amlodipine besylate 5 mg and 10 mg were studied alone and in combination in an 8-week, 1,685-patient, randomized, double-blind, placebo-controlled, multifactorial study. Treatment with aliskiren and amlodipine resulted overall in significantly greater reductions in diastolic and systolic blood pressure compared to the respective monotherapy components as shown in Table 4.

**Table 4: Placebo-Subtracted Reductions in Seated Trough Cuff Blood Pressure in Combination with Amlodipine**

| Aliskiren, mg | Placebo mean change | Amlodipine, mg | | |
|---|---|---|---|---|
| | | 0 | 5 | 10 |
| 0 | 5.4/6.8 | -- | 5.6/9.0 | 8.5/14.3 |
| 150 | -- | 2.6/3.9 | 8.6/13.9 | 10.8/17.1 |
| 300 | -- | 4.9/8.6 | 9.6/15.0 | 11.1/16.4 |

***ACE inhibitors ~~and Amlodipine~~***
Aliskiren has not been studied when added to maximal doses of ACE inhibitors to determine whether aliskiren produces additional blood pressure reduction. ~~with a maximal dose of an ACE inhibitor. Aliskiren 150 mg provided additional blood pressure reduction when coadministered with amlodipine 5 mg in one study, but the combination was not statistically significantly better than amlodipine 10 mg.~~

There are no trials of the Tekturna HCT combination tablet demonstrating reductions in cardiovascular risk in patients with hypertension, but the hydrochlorothiazide component has demonstrated such benefits.

Under **HOW SUPPLIED/ STORAGE AND HANDLING,**

Dispense in ~~a tight~~ original container ~~(USP)~~.

Under **PATIENT COUNSELING INFORMATION,**

"See FDA-approved patient labeling (Patient Information)" was added.

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements and any 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.

**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.

**LETTERS TO HEALTH CARE PROFESSIONALS**

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

**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 Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

*{See appended electronic signature page}*

Mary Ross Southworth, PharmD
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

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/s/

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MARY R SOUTHWORTH
10/12/2011