DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022107/S-021

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Leigh Strachan
Global Program Regulatory Affairs, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Ms. Strachan:

Please refer to your Supplemental New Drug Application (sNDA) dated and received April 6, 2012, 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 (additions are marked as underlined text and deletions are marked as ~~strikethrough~~ text):

In Highlights:

1. Under **RECENT MAJOR CHANGES,** the following was added/~~deleted~~:

Contraindications: Concomitant use with ARBs or ACEIs in diabetes (4)	03/2012
Boxed Warning: Fetal Toxicity	02/2012
~~Indications and Usage: Benefits of lowering blood pressure (1)~~	~~10/2011~~
Warnings and Precautions (5.1)	02/2012
Warnings and Precautions (5.2, 5.4, 5.5, 5.9)	03/2012

2. Under **DOSAGE AND ADMINISTRATION,** the following text was ~~deleted~~:

   - ~~May be administered with other antihypertensive agents. (2.6)~~

3. Under **CONTRAINDICATIONS,** the following was added:

   Do not use with angiotensin receptor blockers (ARBs) or ACE inhibitors (ACEI) in patients with diabetes (4)

4. Under **WARNINGS AND PRECAUTIONS**, the following was added:

   - Avoid concomitant use with ARBs or ACEI in patients with renal impairment (GFR<60 mL/min) (5.2)
   - Head and Neck Angioedema: Discontinue Tekturna HCT and monitor until signs and symptoms resolve. (5.3~~2~~)
   - Hypotension: Correct volume depletion prior to initiation. (5.4~~3~~)
   - Impaired renal function: Monitor serum creatinine periodically .(5.5)

- Hyperkalemia: Monitor potassium levels periodically. (5.9)
- Hydrochlorothiazide has been associated with acute angle-closure glaucoma (5.~~10~~11)

In Full Prescribing Information:

1. Under **DOSAGE AND ADMINISTRATION**, the following text was added:

2.6 Use with Other Antihypertensives
Tekturna HCT may be administered with some other antihypertensive agents. In diabetics, do not use in combination with angiotensin receptor blockers (ARBs) or angiotensin converting enzyme inhibitors (ACEIs) *[(see Contraindications (4)]*. Concomitant use of aliskiren with an ARB or ACEI is not recommended in patients with GFR <60 ml/min *[see Warnings and Precautions (5.2)]* There are no data available with use of Tekturna HCT with angiotensin-converting enzyme inhibitors or beta blockers *[see Clinical Studies (14)]*.

2. Under **CONTRAINDICATIONS**, the following text was added:

Do not use aliskiren with ARBs or ACEIs in patients with diabetes *[see Warnings (5.2), Clinical Trials (14.4)]*.

3. Under **WARNINGS AND PRECAUTIONS**, the following text was added/~~deleted~~:

5.2 Renal Impairment/Hyperkalemia/Hypotension when Tekturna HCT is given in combination with ARBs or ACEI
Tekturna HCT is contraindicated in patients with diabetes who are receiving ARBs or ACEI because of the increased risk of renal impairment, hyperkalemia, and hypotension *[see Contraindications (4) and Clinical Trials (14.3)]*.

Avoid use of Tekturna HCT with ARBs or ACEI in patients with moderate renal impairment (GFR <60 ml/min).

5.~~3~~3 Hypotension ~~in Volume- and/or Salt-Depleted Patients~~
~~An excessive fall in blood pressure (hypotension) was rarely seen (<1%) in patients with uncomplicated hypertension treated with Tekturna HCT in controlled trials.~~ In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur. Correct these conditions prior to administration of Tekturna HCT, or the treatment should start under close medical supervision.
~~If an excessive fall in blood pressure occurs, place the patient in the supine position and, if necessary, given an intravenous infusion of normal saline.~~ A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

5.4 Impaired Renal Function
Monitor renal function periodically in patients treated with Tekturna HCT. Changes in renal function including acute renal failure can be caused by drugs that ~~inhibit~~ affect the renin-angiotensin system and by diuretics. Patients whose renal function may depend in

part on the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, ~~chronic kidney disease,~~ severe ~~congestive~~ heart failure, post-myocardial infarction, or volume depletion) or patients receiving ARB, ACEI, or non-steroidal anti-inflammatory (NSAID) therapy may be at particular risk of developing acute renal failure on Tekturna HCT *[see Contraindications (4), Warnings (5.2), Clinical Trials (14.4)].* ~~Monitor renal function periodically in these patients.~~ Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on Tekturna HCT.

5.8 Serum Electrolyte Abnormalities

Tekturna HCT

In the short-term controlled trials of various doses of Tekturna HCT, in patients with hypertension not concomitantly treated with an ARB or ACEI, the incidence of hypertensive patients who developed hypokalemia (serum potassium <3.5 mEq/L) was 2.2%; the incidence of hyperkalemia (serum potassium >5.5 mEq/L) was 0.8%. No patients discontinued due to increase or decrease of serum potassium.

~~Hydrochlorothiazide can cause hypokalemia and hyponatremia. Hypomagnesemia can result in hypokalemia which appears difficult to treat despite potassium repletion. Drugs that inhibit the renin-angiotensin system can cause hyperkalemia. Monitor serum electrolytes periodically.~~

Aliskiren

Monitor serum potassium periodically in patients receiving aliskiren. Drugs that affect the renin-angiotensin system can cause hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes, combination use with ARBs or ACEI *[see Contraindications (4), Warnings (5.2), and Clinical Trials (14.4)]*, NSAIDs, potassium supplements, or potassium sparing diuretics.

Hydrochlorothiazide

Hydrochlorothiazide can cause hypokalemia and hyponatremia. Hypomagnesemia can result in hypokalemia which appears difficult to treat despite potassium repletion.

If hypokalemia is accompanied by clinical signs (e.g., muscular weakness, paresis, or ECG alterations), Tekturna HCT should be discontinued. Correction of hypokalemia and any coexisting hypomagnesaemia is recommended prior to the initiation of thiazides.

4. Under **ADVERSE REACTIONS**, the following text was added/~~deleted~~:

6.1 Clinical Trials Experience

Aliskiren

Aliskiren has been evaluated for safety in 6,460 patients, including 1,740 treated for longer than 6 months, and 1,250 for longer than 1 year. In placebo-controlled clinical trials, discontinuation of therapy due to a clinical adverse event, including uncontrolled hypertension occurred in 2.2% of patients treated with aliskiren, versus 3.5% of patients given placebo. These data do not include information from the ALTITUDE study which evaluated the use of aliskiren in combination with ARBs or ACEI *[see Contraindications (4), Warnings (5.2), and Clinical Trials (14.4)].*

Two cases of angioedema with respiratory symptoms were reported with aliskiren use in the clinical studies. Two other cases of periorbital edema without respiratory symptoms were reported as possible angioedema and resulted in discontinuation. The rate of these angioedema cases in the completed studies was 0.06%.

In addition, 26 other cases of edema involving the face, hands, or whole body were reported with aliskiren use, including 4 leading to discontinuation.

In the placebo-controlled studies, however, the incidence of edema involving the face, hands, or whole body was 0.4% with aliskiren compared with 0.5% with placebo. In a long-term active-controlled study with aliskiren and HCTZ arms, the incidence of edema involving the face, hands, or whole body was 0.4% in both treatment arms.

Aliskiren produces dose-related gastrointestinal (GI) adverse reactions. Diarrhea was reported by 2.3% of patients at 300 mg, compared to 1.2% in placebo patients. In women and the elderly (age ≥65) increases in diarrhea rates were evident starting at a dose of 150 mg daily, with rates for these subgroups at 150 mg comparable to those seen at 300 mg for men or younger patients (all rates about 2% to 2.3%). Other GI symptoms included abdominal pain, dyspepsia, and gastroesophageal reflux, although increased rates for abdominal pain and dyspepsia were distinguished from placebo only at 600 mg daily. Diarrhea and other GI symptoms were typically mild and rarely led to discontinuation.

Aliskiren was associated with a slight increase in cough in the placebo-controlled studies (1.1% for any aliskiren use vs. 0.6% for placebo). In active-controlled trials with ACE inhibitor (ramipril, lisinopril) arms, the rates of cough for the aliskiren arms were about one-third to one-half the rates in the ACE inhibitor arms.

Other adverse reactions with increased rates for aliskiren compared to placebo included rash (1% vs. 0.3%) and renal stones (0.2% vs. 0%).

Single episodes of tonic-clonic seizures with loss of consciousness were reported in two patients treated with aliskiren in the clinical trials. One patient had predisposing causes for seizures and had a negative electroencephalogram (EEG) and cerebral imaging following the seizures; for the other patient, EEG and imaging results were not reported. Aliskiren was discontinued and there was no rechallenge in either case.

~~The following adverse events occurred in placebo-controlled clinical trials at an incidence of more than 1% of patients treated with aliskiren, but also occurred at about the same or greater incidence in patients receiving placebo: headache, nasopharyngitis, dizziness, fatigue, upper respiratory tract infection, back pain and cough.~~

No clinically meaningful changes in vital signs or in ECG (including QTc interval) were observed in patients treated with aliskiren.

Clinical Laboratory Test Abnormalities

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Tekturna HCT <u>in patients with hypertension not concomitantly treated with an ARB or ACEI.</u>

<u>*Blood Urea Nitrogen (BUN)/Creatinine:*</u> ~~Elevations~~ <u>In patients with hypertension not concomitantly treated with an ARB or ACEI, elevations</u> (greater than 50% increase) in BUN and creatinine occurred in 11.8% and 0.9%, respectively, of patients taking Tekturna HCT, and 7% and 1.1%, respectively, of patients given placebo in short-term

controlled clinical trials. No patients were discontinued due to an increase in either BUN or creatinine.

6.2 Post-Marketing Experience

~~*Blood creatinine increased*~~

5. Under **DRUG INTERACTIONS**, the following text was added/~~deleted~~:

~~No drug interaction studies have been conducted with Tekturna HCT and other drugs, although studies with the individual aliskiren and hydrochlorothiazide components are described below.~~

Aliskiren

Cyclosporine: Avoid co-administration of cyclosporine with aliskiren.

Itraconazole: Avoid co-administration of itraconazole with aliskiren. *[See Clinical Pharmacology (12.3).]*

Non-Steroidal Anti-Inflammatory Agents (NSAIDs) including selective Cyclooxygenase 2 inhibitors (COX-2 inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors with agents that affect ~~acting on~~ the renin-angiotensin system, including aliskiren, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving aliskiren and NSAID therapy.

The antihypertensive effect of ~~agents acting on the renin-angiotensin system, including~~ aliskiren, may be attenuated by NSAIDs.

6. Under **CLINICAL STUDIES**, the following section was added:

14.4 Aliskiren in Patients with Diabetes treated with ARB or ACEI (ALTITUDE study)

Patients with diabetes with renal disease (defined either by the presence of albuminuria or reduced GFR) were randomized to aliskiren 300 mg daily (n=4283) or placebo (n=4296). All patients were receiving background therapy with an ARB or ACEI. The primary efficacy outcome was the time to the first event of the primary composite endpoint consisting of cardiovascular death, resuscitated sudden death, non-fatal myocardial infarction, non-fatal stroke, unplanned hospitalization for heart failure, onset of end stage renal disease, renal death, and doubling of serum creatinine concentration from baseline sustained for at least one month. After a median follow up of about 27 months, the trial was terminated early for lack of efficacy. Higher risk of renal impairment, hypotension and hyperkalemia was observed in aliskiren compared to placebo treated patients, as shown in the table below.

Table 5. Incidence of selected adverse events in ALTITUDE

	Aliskiren N=4283		Placebo N=4296	
	Serious Adverse Events* (%)	Adverse Events (%)	Serious Adverse Events* (%)	Adverse Events(%)
Renal impairment †	4.7	12.4	3.3	10.4
Hypotension ††	2.0	18.6	1.7	14.8
Hyperkalemia †††	1.1	36.9	0.3	27.1

†renal failure, renal failure acute, renal failure chronic, renal impairment

††dizziness, dizziness postural, hypotension, orthostatic hypotension, presyncope, syncope

††† Given the variable baseline potassium levels of patients with renal insufficiency on dual RAAS therapy, the reporting of adverse event of hyperkalemia was at the discretion of the investigator.

* A Serious Adverse Event (SAE) is defined as: an event which is fatal or life-threatening, results in persistent or significant disability/incapacity, constitutes a congenital anomaly/birth defect, requires inpatient hospitalization or prolongation of existing hospitalization, or is medically significant (i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes previously listed).

The risk of stroke (2.7% aliskiren vs 2.0% placebo) and death (6.9% aliskiren vs. 6.4% placebo) were also numerically higher in aliskiren treated patients.

The following changes were made to the Patient Package Insert (PPI):

1. Under **Who should not take Tekturna?**, the following text was added:

   - **If you have diabetes and are taking a kind of medicine called an angiotensin-receptor-blocker or angiotensin-converting-enzyme-inhibitor .**

2. Under **What Should I Tell My Doctor Before Taking Tekturna?**, the bullets were re-ordered.

3. Under **Tell your doctor about all the medicines you take,** the following text was added/~~deleted~~:

   - a kind of medicine called angiotensin receptor blocker or angiotensin converting enzyme inhibitor
   - ~~other medicines for high blood pressure or a heart problem.~~

4. Under **What Are Possible Side Effects Of Tekturna?,** the following was added as the last bullet:

   - high levels of potassium in the blood (hyperkalemia)

5. Editorial changes were made throughout the label (the Table of Contents was updated, the numbers in **WARNINGS AND PRECAUTIONS** were updated, tables were re-numbered)

6. The revision date and version number were updated.

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

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
04/16/2012