



NDA 021985/S-023

SUPPLEMENT APPROVAL

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

Dear Dr. Chan:

Please refer to your Supplemental New Drug Application (sNDA) dated and received April 5, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tekturna (aliskiren) 150 mg and 300 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 ~~striketrough~~ text):

In Highlights:

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

<u>Contraindications: Concomitant use with ARBs or ACEIs in diabetes (4)</u>	<u>01/2012</u>
<u>Boxed Warning: Fetal Toxicity</u>	<u>02/2012</u>
<u>Warning and Precautions (5.2, 5.4, 5.5, 5.6)</u>	<u>01/2012</u>
Indications and Usage: Benefits of lowering blood pressure (1.1)	10/2011
Warnings and Precautions, Cyclosporine or Itraconazole (5.7)	02/2011

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

- ~~Majority of effect of given dose substantially attained in 2 weeks (2.1)~~
- ~~May be administered with other anti-hypertensive agents (2.2)~~
- ~~Additive effects with angiotensin converting enzyme inhibitors (ACEI) at maximal doses have not been studied (2.2)~~
- Starting dose: 150 mg once daily with a routine pattern with regard to meals. If blood pressure remains uncontrolled titrate up to 300 mg daily (2.1, 2.3)
- Majority of effect of given dose attained in 2 weeks (2.1)
- ~~No initial dosage adjustment required in the elderly, in patients with mild to severe renal or hepatic impairment. (2.4, 12.3)~~

3. Under **CONTRAINDICATIONS**, the following was added/~~deleted~~:

~~None (4)~~

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/deleted:
- ~~Avoid neonatal/fetal exposure (5.1)~~
 - Avoid concomitant use with ARBs or ACEI in patients with renal impairment (GFR<60 mL/min) (5.4)
 - Head and neck angioedema. Discontinue use of Tekturna and monitor until signs and symptoms resolve (5.23)
 - Hypotension in volume and/or salt depleted patients: Correct imbalances before initiating therapy with Tekturna (5.34)
 - Impaired renal function: Monitor serum creatinine periodically (5.5).
 - Hyperkalemia: Monitor potassium levels periodically ~~Caution should be exercised when co-administered with ACEI, potassium sparing diuretics, potassium supplements or other potassium containing salt substitutes (5.5)~~
5. Under **DRUG INTERACTIONS**, the following text was added/deleted:
- NSAIDS use may lead to increased risk of renal impairment and loss of antihypertensive effect.

In Full Prescribing Information:

1. Under **INDICATIONS AND USAGE**, the following text was ~~deleted~~ from the end of the section:

~~Tekturna may be used alone or in combination with other antihypertensive agents. Use with maximal doses of ACE inhibitors has not been adequately studied.~~

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

2.2 Use with Other Antihypertensives

Tekturna 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 aliskirin with an ARB or ACEI is not recommended in patients with GFR <60 ml/min [see Warnings and Precautions (5.2)] Most exposure to date is with diuretics, an angiotensin receptor blocker (valsartan) or a calcium channel blocker (amlodipine). Aliskiren used together with these drugs has a greater effect at their maximum recommended doses than either drug alone. It is not known whether additive effects are present when Tekturna is used with angiotensin-converting enzyme inhibitors (ACEI) or beta blockers (BB).

2.4 Dosing in Special Populations

~~No adjustment of the starting dose is required in elderly patients, patients with mild to severe renal impairment or mild to severe hepatic insufficiency. However, clinical experience in patients with severe renal impairment is limited [See Clinical Pharmacology (12.3) and Warnings and Precautions (5.4)].~~

3. Under **CONTRAINDICATIONS**, the following text was added/deleted:

~~None. Do not use aliskiren with ARBs or ACEIs in patients with diabetes [see Warnings (5.2), Clinical Trials (14.3)].~~

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

5.2 Renal Impairment/Hyperkalemia/Hypotension when Tekturna is given in combination with ARBs or ACEI

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

5.43 Hypotension

~~An excessive fall in blood pressure was rarely seen (0.1%) in patients with uncomplicated hypertension treated with Tekturna alone in controlled trials and in <1% during combination therapy with other antihypertensive agents. In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those receiving high doses of diuretics), symptomatic hypotension may occur after initiation of treatment with Tekturna. This condition should be corrected prior to administration of Tekturna, or the treatment should start under close medical supervision.~~

~~If an excessive fall in blood pressure occurs, the patient should be placed 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.~~

5.54 Impaired Renal Function

~~Patients with greater than moderate renal dysfunction (creatinine 1.7 mg/dL for women and 2.0 mg/dL for men and/or estimated GFR <30 ml/min), a history of dialysis, nephrotic syndrome, or renovascular hypertension were excluded from clinical trials of Tekturna in hypertension. Consider periodic determinations of serum electrolytes to detect possible electrolyte imbalances particularly in patients with severe renal impairment.~~

Monitor renal function periodically in patients treated with Tekturna. Changes in renal function, including acute renal failure, can be caused by drugs that affect the renin-angiotensin system. Patients whose renal function may depend in part on the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, severe 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 for developing acute renal failure on Tekturna [see Contraindications (4), Warnings (5.2), Clinical Trials (14.3)]. Consider

withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function.

5.65 Hyperkalemia

~~Increases in serum potassium >5.5 mEq/L were infrequent with Tekturna alone (0.9% compared to 0.6% with placebo). However, when used in combination with an ACE inhibitor in a diabetic population, increases in serum potassium were more frequent (5.5%). Routine monitoring of electrolytes and renal function is indicated in this population.~~

~~Concomitant use of Tekturna with potassium sparing diuretics, potassium supplements, salt substitutes containing potassium, or other drugs that increase potassium levels may lead to increases in serum potassium.~~

Monitor serum potassium periodically in patients receiving Tekturna. 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 (14.3)], NSAIDs, or potassium supplements or potassium sparing diuretics.

5.6 Renal Artery Stenosis

~~No data are available on the use of Tekturna in patients with unilateral or bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.~~

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

6.1 Clinical Trials Experience

Data described below reflect the evaluation of the safety of Tekturna in more than 6,460 patients, including over 1,740 treated for longer than 6 months, and more than 1,250 patients 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 Tekturna vs. 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 (14.3)].

~~The following adverse events occurred in placebo controlled clinical trials at an incidence of more than 1% of patients treated with Tekturna, 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.~~

Clinical Laboratory Findings

In controlled clinical trials, clinically relevant changes in standard laboratory parameters were rarely associated with the administration of Tekturna in patients with hypertension not concomitantly treated with ARB or ACEI. In multiple-

dose studies in hypertensive patients, Tekturna had no clinically important effects on total cholesterol, HDL, fasting triglycerides, or fasting glucose, ~~or uric acid~~.

Blood Urea Nitrogen, Creatinine: ~~Minor~~ In patients with hypertension not concomitantly treated with an ARB or ACEI, minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 7% of patients ~~with essential hypertension~~ treated with Tekturna alone vs. 6% on placebo [*see Warnings (5.2)*].

Serum Potassium: In patients with hypertension not concomitantly treated with and ARB or ACEI, increases in serum potassium >5.5 mEq/L were infrequent ~~in patients with essential hypertension treated with Tekturna alone~~ (0.9% compared to 0.6% with placebo). ~~However, when used in combination with an angiotensin-converting enzyme inhibitor (ACEI) in a diabetic population increases in serum potassium were more frequent (5.5%) and routine monitoring of electrolytes and renal function is indicated in this population.~~ [*see Contraindications (4) and Warnings and Precautions (5.6)*].

6.2 Postmarketing Experience

The following adverse reactions have been reported in aliskiren post-marketing experience. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity: angioedema requiring airway management and hospitalization

Peripheral edema

Blood creatinine increased

6. Under **DRUG INTERACTIONS**, the following text was added:

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 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 aliskiren may be attenuated by NSAIDs.

7. Under **USE IN SPECIFIC POPULATIONS**, the following section was added:

8.6 Renal impairment

Safety and effectiveness of Tekturna in patients with severe renal impairment (CrCL <30 ml/min) have not been established as patients with eGFR <30ml/min were excluded in clinical trials [*see Clinical Trials (14)*].

8. Under **CLINICAL PHARMACOLOGY**, the following text was added/deleted:

Special Populations

Renally Impaired Patients: Aliskiren was evaluated in patients with varying degrees of renal insufficiency. The rate and extent of exposure (AUC and C_{max}) of aliskiren in subjects with renal impairment did not show a consistent correlation with the severity of renal impairment. Adjustment of the starting dose is not required in these patients [*see Warnings (5.2)*] [~~*see Dosage and Administration (2.4)*~~].

Hepatically Impaired Patients: The pharmacokinetics of aliskiren were not significantly affected in patients with mild to severe liver disease. Consequently, adjustment of the starting dose is not required in these patients [~~*see Dosage and Administration (2.4)*~~].

Pediatric Patients: The pharmacokinetics of aliskiren have not been investigated in patients <18 years of age [~~*see Dosage and Administration (2.4)*~~].

Geriatric Patients: Exposure (measured by AUC) is increased in elderly patients ≥65 years. Adjustment of the starting dose is not required in these patients [~~*see Dosage and Administration (2.4)*~~].

9. Under **CLINICAL STUDIES**, the following text was added:

14.3 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

	<u>Aliskiren</u> <u>N=4283</u>		<u>Placebo</u> <u>N=4296</u>	
	<u>Serious</u> <u>Adverse</u> <u>Events* (%)</u>	<u>Adverse Events</u> <u>(%)</u>	<u>Serious</u> <u>Adverse</u> <u>Events* (%)</u>	<u>Adverse</u> <u>Events(%)</u>
<u>Renal</u> <u>impairment</u> †	<u>4.7</u>	<u>12.4</u>	<u>3.3</u>	<u>10.4</u>
<u>Hypotension</u> <u>††</u>	<u>2.0</u>	<u>18.6</u>	<u>1.7</u>	<u>14.8</u>

<u>Hyperkalemia</u> †††	<u>1.1</u>	<u>36.9</u>	<u>0.3</u>	<u>27.1</u>
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† 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:
 - 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. The Table of Contents was updated to reflect the recent changes.
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