



NDA 021985 / S-019

**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 15, 2011, received April 15, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tekurna (aliskiren) 150 mg, 300 mg tablets.

This letter supersedes the approval letter mailed to you on October 12, 2011, the labeling attached to that letter contained a blank page 5. The missing text is now included.

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,

- The treatment of hypertension, to lower blood pressure (1.1)

Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.

Under **HL, DOSAGE AND ADMINISTRATION**

The “General Considerations” and “Hypertension” subheadings have been deleted.

Angiotensin-converting enzyme inhibitors has been spelled out at its first use.

The **CONTRAINDICATIONS** section has been added to HL.

-----**CONTRAINDICATIONS**-----

None (4)

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 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. There are no controlled trials demonstrating risk reduction with Tekturna.

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.

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

Under **DOSAGE AND ADMINISTRATION,**

**2.2 Use with Other Antihypertensives**

Tekturna may be administered with other antihypertensive agents. Most exposure to date is with diuretics, an angiotensin receptor blocker (valsartan) or a calcium channel blocker (amlodipine), and Aliskiren used together with these drugs together have 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 ~~care should be taken when dosing Tekturna in patients with severe renal impairment, as clinical experience with such patients is limited.~~ [See *Clinical Pharmacology* (12.3) and *Warnings and Precautions* (5.4).]

Under **WARNINGS AND PRECAUTIONS,**

**5.5 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. ~~If concomitant use is considered necessary, caution should be exercised.~~

Under **ADVERSE REACTIONS,**

“effects” was changed to “reactions” under the *Gastrointestinal* section.

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 **USE IN SPECIAL POPULATIONS,**

**8.5 Geriatric Use**

Of the total number of patients receiving aliskiren in clinical studies, 1,275 (19%) were 65 years or older and 231 (3.4%) were 75 years or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. ~~Blood pressure response and adverse effects were generally similar to those in younger patients.~~

Under **DESCRIPTION,**

The sentence, “Tekturna contains aliskiren hemifumarate, a renin inhibitor, that is provided as tablets for oral administration” was added.

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**

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

***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 co-administered with amlodipine 5 mg in one study, but the combination was not statistically significantly better than amlodipine 10 mg.~~

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