



NDA 200045/S-012

**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 Amturnide (aliskiren/amlodipine besylate/hydrochlorothiazide) 150/5/12.5 mg, 300/5/12.5 mg, 300/5/25 mg, 300/10/12.5 mg, and 300/10/25 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 ~~strickethrough 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>03/2012</u> |
| <u>Boxed Warning: Fetal Toxicity</u>   | <u>02/2012</u> |
| <u>Indications and Usage: Benefits of lowering blood pressure (1)</u>        | <u>10/2011</u> |
| <u>Warnings and Precautions (5.1, 5.14)</u>                                  | <u>02/2012</u> |
| <u>Warning and Precautions (5.2, 5.4, 5.6, 5.11)</u>                         | <u>03/2012</u> |
| <u>Warnings and Precautions, Cyclosporine or Itraconazole (5.11)</u>         | <u>04/2011</u> |

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

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

3. 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)
- Impaired renal function: Monitor serum creatinine periodically . (5.6)
- Hyperkalemia: Monitor potassium levels periodically. (5.8)

*In Full Prescribing Information:*

1. 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)].

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

### **5.2 Renal Impairment/Hyperkalemia/Hypotension when Amturnide is given in combination with ARBs or ACEI**

Amturnide 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 (14.2)].

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

### **5.43 Hypotension**

~~An excessive fall in blood pressure (hypotension) was rarely seen (b) (4) in patients with uncomplicated hypertension treated with Amturnide in a controlled trial. 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, give 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.~~

### **5.6 Impaired Renal Function**

~~Monitor renal function periodically in patients treated with Amturnide. 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 (14.2)]. ~~Monitor renal function periodically in these patients.~~ Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on Amturnide.~~

### **5.11 Serum Electrolyte Abnormalities**

#### *Amturnide*

In a short-term controlled trial the incidence of patients with hypertension not concomitantly treated with an ARB or ACEI, who developed hypokalemia (serum potassium <3.5 mEq/L) was 11.0% of Amturnide-treated patients compared to 19.0% of amlodipine/HCTZ patients, 4.4% of aliskiren/HCTZ patients, and 2.1% of aliskiren/amlodipine patients; the incidence of hyperkalemia (serum potassium >5.5

mEq/L) was 3.0% compared to 2.0% of amlodipine/HCTZ patients, 0.7% of aliskiren/HCTZ patients, and 0.7% of aliskiren/amlodipine patients. No Amturnide-treated patients discontinued due to increase or decrease of serum potassium.

#### 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, or 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. ~~Drugs that inhibit the renin-angiotensin system can cause hyperkalemia. Monitor serum electrolytes periodically.~~

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

3. 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)].

##### **Clinical Laboratory Test Abnormalities**

Clinical laboratory findings for Amturnide in patients with hypertension not concomitantly treated with an ARB or ACEI were obtained in a controlled trial of Amturnide administered at the maximal dose of 300/10/25 mg compared to maximal doses of dual therapies, i.e., aliskiren/amlodipine 300/10 mg, aliskiren/HCTZ 300/25 mg and amlodipine/HCTZ 10/25 mg.

##### **Blood Urea Nitrogen (BUN)/Creatinine**

No patients with hypertension not concomitantly treated with an ARB or ACEI treated with Amturnide had elevations in BUN >40 mg/dL or creatinine >2.0 mg/dL.

#### **6.2 Post-Marketing Experience**

*Aliskiren:*

*Hypersensitivity:* angioedema requiring airway management and hospitalization. Peripheral edema, ~~Blood creatinine increased~~ severe cutaneous adverse reactions, including Stevens Johnson syndrome and toxic epidermal necrolysis.

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



**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.

5. Under **CLINICAL STUDIES**, the following section 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.

Table5. Incidence of selected adverse events in ALTITUDE

|  | <u>Aliskiren</u> | <u>Placebo</u> |
|--|------------------|----------------|
|  | <u>N=4283</u>    | <u>N=4296</u>  |

|                           | <u>Serious Adverse Events* (%)</u> | <u>Adverse Events (%)</u> | <u>Serious Adverse Events* (%)</u> | <u>Adverse Events(%)</u> |
|---------------------------|------------------------------------|---------------------------|------------------------------------|--------------------------|
| <u>Renal impairment</u> † | <u>4.7</u>                         | <u>12.4</u>               | <u>3.3</u>                         | <u>10.4</u>              |
| <u>Hypotension</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>              |

† 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 Amturnide?**, 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 **Especially tell your doctor if you are taking:**, 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.
3. Under **The most common side effects of Amturnide include:**, the following was added:
  - Common side effects of Amturnide include:
  - diarrhea
  - cough

- tiredness
  - high levels of potassium in the blood (hyperkalemia)
4. The Table of Contents was updated to reflect the recent changes.
  5. The section numbers were updated throughout.
  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 Effectuated” (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

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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  
04/18/2012