DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200045/S-014

**SUPPLEMENT APPROVAL**

Novartis Pharmaceutical Corporation
Attention: Leigh Strachan
Global Program Regulatory Manager
One Health Plaza
East Hanover, NJ 07936

Dear Ms. Strachan:

Please refer to your Supplemental New Drug Application (sNDA) dated and received March 19, 2013, 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, 300/5012.5 mg, 300/5/25 mg, 300/10/12.5 mg, and 300/10/25 mg Tablets.

We also acknowledge your submission dated May 3, 2013.

This supplemental new drug application provides for labeling revised as follows (additions are marked as underlined text and deletions are marked as ~~strikethrough text~~):

1. In **HIGHLIGHTS/RECENT MAJOR CHANGES**, the following text was added/deleted:

~~Boxed Warning: Fetal Toxicity 02/2012~~
~~Contraindications: Concomitant use with ARBs and ACEIs in diabetes (4) 03/2102~~
~~Warning and Precautions (5.1, 5.13) 02/2012~~
~~Warnings and Precautions (5.2, 5.4, 5.6, 5.10) 03/2012~~
~~Warnings and Precautions (5.3) 09/2012~~
Warnings and Precautions (5.4) 10/2013

2. In **HIGHLIGHTS/WARNINGS AND PRECAUTIONS,** the following text was added to the third bullet:

- Hypotension: ~~Correct volume depletion prior to initiation~~ in volume and/or salt depleted patients or with combined use of other agents acting on RAAS: Correct imbalances before initiating therapy with Amturnide (5.4)

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

> Symptomatic hypotension may occur after initiation of treatment with Amturnide in patients with marked volume depletion, patients with salt depletion, or with combined use of aliskiren and other agents acting on the renin-angiotensin-aldosterone system. The volume or salt depletion should be corrected prior to administration of Amturnide, or the treatment should start under close medical supervision. ~~In patients with an activated renin-angiotensin-aldosterone system, such as volume- and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur in patients receiving renin-angiotensin-aldosterone system (RAAS) blockers. Correct these conditions prior to administration of Amturnide, or start the treatment under close medical supervision.~~

4. Under **ADVERSE REACTIONS/Postmarketing Experience**, the following text was added to the fourth paragraph:

> Peripheral edema, severe cutaneous adverse reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, urticaria, hepatic enzyme increase with clinical symptoms of hepatic dysfunction, pruritus, erythema

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

> *Dual Blockade of the renin-angiotensin-aldosterone system:* The concomitant use of aliskiren with other agents acting on the renin-angiotensin-aldosterone system such as ACEIs or ARBs is associated with an increased risk of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy . Monitor blood pressure, renal function, and electrolytes in patients on aliskiren and other agents that affect the renin-angiotensin-aldosterone system *[see Warnings and Precautions (5.4, 5.6, 5.10)]*.
>
> The concomitant use of aliskiren with an ARB or an ACEI in diabetic patients is contraindicated and should be avoided in patients with moderate renal impairment *[see Contraindications (4) and Warnings and Precautions (5.2)]*.
>
> *Furosemide:* Oral co-administration of aliskiren and furosemide reduced exposure to furosemide. Monitor diuretic effects when furosemide is co-administered with aliskiren.

6. Under **CLINICAL PHARMACOLOGY/*Drug Interactions***, the following text was added under Figure 2:

> Furosemide: In patients with heart failure, co-administration of aliskiren (300 mg/day) reduced plasma AUC and Cmax of oral furosemide (60 mg/day) by 17% and 27%, respectively, and reduced 24 hour urinary furosemide excretion by 29%. This change in exposure did not result in statistically significant difference in total urine volume and urinary sodium excretion over 24 hours. However, a transient decrease in urinary sodium excretion and urine volume effects up to 12 hours were observed when furosemide was co-administered with aliskiren 300 mg/day.

7. In sections 5.6, 5.10, and 7 of the label, the word "aldosterone" was added after the words renin-angiotensin to read: "renin-angiotensin-aldosterone system".

***The sponsor made the following changes to the Patient Package Insert:***

1. Under **What Are Possible Side Effects Of Amturnide?**, the following text was added:

- **Renal impairment or failure**. Aliskiren, one of the medicines in Amturnide, may cause renal disorder with symptoms such as severely decreased urine output or decreased urine output (signs of renal impairment or failure).

Less common side effects include rash, severe skin reactions (signs may include severe blistering of the lips, eyes or mouth, rash with fever and skin peeling) and liver disorder (signs may include nausea, loss of appetite, dark colored urine or yellowing of skin and eyes).

2. 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, as amended, 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, PharmD.
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
11/04/2013