DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022545/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 Tekamlo (aliskiren/amlodipine besylate) 150/5 mg, 150/10 mg, 300/5 mg, and 300/10 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)	03/201
Boxed Warning: Fetal Toxicity	02/2012
~~Indications and Usage: Benefits of lowering blood pressure (1)~~	~~10/2011~~
Warnings and Precautions: Fetal Toxicity (5.1)	02/2012
Warning and Precautions (5.2, 5.4, 5.6, 5.10)	03/2012
~~Warnings and Precautions: Cyclosporine or Itraconazole (5.9)~~	~~04/2011~~

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

~~• May administer with other antihypertensive agents. (2.7)~~
~~• Additive effects with ACE inhibitors at maximal doses have not been studied.~~

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

~~None~~
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 fetal and neonatal exposure. (5.1)~~

- Avoid concomitant use with ARBs or ACEI in patients with renal impairment (GFR<60 mL/min). (5.2)
- Head and neck angioedema: Discontinue Tekamlo and monitor until signs and symptoms resolve. (5.32)
- Hypotension in volume- and/or salt-depleted patients: Correct imbalances before initiating therapy with Tekamlo. (5.43)
- Increased angina or myocardial infarction with calcium channel blockers may occur upon dosage initiation or increase. (5.54)
- Impaired renal function: Monitor serum creatinine periodically. (5.5-6) ~~Patients with renal impairment: Decrease in renal function may be anticipated with susceptible individuals. (5.5)~~
- Patients with hepatic impairment: Titrate slowly. (5.76)
- Patients with heart failure: Titrate slowly. (5.87)
- Hyperkalemia: Monitor ~~serum~~ potassium levels periodically (5.10) ~~when co-administering with ACEI, potassium-sparing diuretics, potassium supplements, or other potassium-containing salt substitutes.~~

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

~~Aliskiren:~~
• Cyclosporine: Avoid concomitant use (7, 12.3)
• Itraconazole: Avoid concomitant use (7, 12.3)
• NSAIDS use may lead to increased risk of renal impairment and loss of antihypertensive effect (7)
~~Amlodipine:~~
• If simvastatin is co-administered with amlodipine, do not exceed doses greater than 20 mg daily of simvastatin (7)

In Full Prescribing Information:

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

2.7 Use with Other Antihypertensives
Tekamlo 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)]* It is not known whether Tekamlo decreases blood pressure further when added to maximum dosages of ACE inhibitors and beta blockers *[see Clinical Studies (14)]*.

~~2.9 Dosing in Specific Populations~~
~~Renal Impairment~~
~~Adjustment of the starting dose is not required in patients with mild to moderate renal impairment. Clinical experience with dosing Tekamlo in patients with moderate renal impairment is limited. No data are available in patients with severe renal impairment *[see Warnings and Precautions (5.5)]*.~~
~~Hepatic Impairment~~

~~No initial dosage adjustment is required for patients with mild or moderate liver insufficiency. Titrate slowly in patients with hepatic impairment *[see Warnings and Precautions (5.6)]*.~~
~~*Elderly Patients*~~
~~Adjustment of the starting dose is not required for elderly patients.~~

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 (14.2)]*.~~None.~~

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

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

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

5.4~~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 Tekamlo 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 Tekamlo, 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.

5.6~~5~~ Impaired Renal Function

Monitor renal function periodically in patients treated with Tekamlo. 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 Tekamlo *[see Contraindications (4), Warnings (5.2), Clinical Trials (14.2)]*. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function.

~~*Tekamlo*~~
~~Clinical trials with Tekamlo in hypertension excluded patients with severe renal impairment.~~
~~*Aliskiren*~~
~~Clinical trials of aliskiren in hypertension excluded patients with severe 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. Consider periodic determinations of serum electrolytes to detect possible electrolyte imbalances.~~

~~5.8 Renal Artery Stenosis~~
~~No data are available on the use of Tekamlo or aliskiren in patients with unilateral or bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. However, in studies of ACE inhibitors in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported.~~

5.10 Hyperkalemia
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 (14.2)]*, NSAIDs, or potassium supplements or potassium sparing diuretics.

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)]*.

Clinical Laboratory Test Abnormalities

In patients with hypertension not concomitantly treated with an ARB or ACEI, elevations in BUN (> 40 mg/dL) and creatinine (>2.0 mg/dL) in patients treated with Tekamlo were <1.0%.

Serum Potassium: In patients with hypertension not concomitantly treated with an ARB or ACEI, increases in serum potassium >5.5 mEq/L were infrequent ~~in patients with essential hypertension treated with both Tekamlo and aliskiren monotherapy~~ (0.9% compared to 0.6% with placebo) *[see Contraindications (4) and Warnings and Precautions (5.10)]*. ~~However, when aliskiren was used in combination with an~~

~~angiotensin-converting enzyme inhibitor (ACEI) in a diabetic population, increases in serum potassium were more frequent (5.5%).~~

~~Monitor electrolytes and renal function in this population.~~

6.2 Post-Marketing Experience

Aliskiren: Peripheral edema, ~~*Blood creatinine increased*~~ severe cutaneous adverse reactions, including Stevens Johnson syndrome and toxic epidermal necrolysis

5. 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~~s~~.

6. Under **USE IN SPECIFIC POPULATIONS**, the following text was added:

8.6 Renal impairment
Safety and effectiveness of Tekamlo in patients with severe renal impairment (CrC1 ≤ 30 mL/min) have not been established as patients with eGFR <30ml/min were excluded in clinical trials *[see Clinical Trials (14)]*.

7. 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.

Table5. 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 Tekamlo?**, 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 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.~~

3. Under **The most common side effects of Tekamlo include:,** the following text was added:

   Common side effects of Tekamlo include:

   - diarrhea
   - cough
   - dizziness
   - flu-like symptoms
   - tiredness
   - high levels of potassium in the blood (hyperkalemia)

4. The Table of Contents was updated to reflect the recent changes.
5. In **CLINICAL PHARMACOLOGY/Pharmacokinetics**, several of the cross references were updated from *[see Dosage and administration]* to *[see Warnings and Precautions],* to reflect the new information.
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