DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022545/S-016

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Annemarie Van der Merwe
Global Program Regulatory Director
One Health Plaza
East Hanover, NJ 07936

Dear Ms. Van der Merwe:

Please refer to your Supplemental New Drug Application (sNDA) dated and received July 25, 2014, 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 supplemental new drug application provides for labeling revised as follows (additions are marked as underlined text and deletions are marked as ~~strikethrough text~~):

In the Package Insert:

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

Dosage and Administration (2.1)	X/2014
~~Warnings and Precautions (5.4)~~	~~11/2013~~

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

- Avoid concomitant use with ARBs or ACEIs particularly~~ACEI~~ in patients with renal impairment [creatinine clearance (CrCl) ~~(GFR~~<60 mL/min].~~)~~ (5.2, 5.4)~~)~~
- Anaphylactic Reactions and ~~Head and Neck~~ Angioedema.~~: Discontinue Tekamlo and monitor until signs and symptoms resolve.~~ (5.3)
- Hypotension: Correct imbalances ~~-~~in volume- and/or salt-depleted patients- (b) (4) ~~Correct imbalances before initiating therapy with Tekamlo~~. (5.4)
- Increased angina or myocardial infarction ~~with calcium channel blockers~~ may occur upon dosage initiation or increase in amlodipine.~~.~~ (5.5)
- Impaired Renal Function~~renal function~~: Monitor serum creatinine periodically. (5.6)
- Hyperkalemia: Monitor potassium levels periodically..~~.~~ (5.8)

3. In **HIGHLIGHTS/DRUG INTERACTIONS**, the following text was added/deleted:

Cyclosporine or Itraconazole: Avoid concomitant use. (5.7, ~~7~~7, 12.3)

(b) (4)

NSAIDs): ~~use may lead to~~ Increased [AV1] ~~increased~~ risk of renal impairment and loss of antihypertensive effect. (7)

If ~~s~~Simvastatin: Avoid ~~simvastatin is coadministeredco-administered with amlodipine, do not exceed~~ doses greater than 20 mg daily. ~~of simvastatin~~ (7)

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

~~**2.4 Use with Other Antihypertensive Drugs**~~

~~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.~~5~~4 Relationship to Meals

~~Advise p~~Patients ~~to~~ should establish a routine pattern for taking Tekamlo, either with or without a ~~regard to~~ meals. High-fat meals decrease absorption substantially *[see Clinical Pharmacology (12.3)]*.

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

5.2 Renal Impairment/Hyperkalemia/Hypotension when Tekamlo is ~~given~~Given in ~~combination~~Combination with ARBs or ACEIs

Tekamlo is contraindicated in patients with diabetes who are receiving ARBs or ACEIs because of the increased risk of renal impairment, hyperkalemia, and hypotension. In general, avoid combined use of aliskiren with ACE inhibitors or ARBs, particularly in patients with creatinine clearance (CrCl) less than ~~<~~ 60 mL ~~/~~/min [AV2] *[see Contraindications (4), Drug Interactions (7) and Clinical Studies (14.3)]*. ~~*2)]*.~~

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

5.6 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 RAAS. ~~renin-angiotensin-aldosterone system.~~ Patients whose renal function may depend in part on the activity of the RAAS ~~renin-angiotensin-aldosterone system~~ (e.g., patients with renal artery stenosis, severe heart failure, post-myocardial infarction or volume depletion) or patients receiving ARB, ACEI or nonsteroidal ~~non-steroidal~~ anti-inflammatory drug (NSAID, including selective Cyclooxygenase-2 inhibitors (COX-2 inhibitors), ~~)~~ therapy may be at particular risk for developing acute renal failure on Tekamlo *[see ~~Contraindications (4),~~ Warnings and Precautions (5.2), Drug Interactions (7), and Use in Specific Populations (8.7), and Clinical Studies (14.2)]*. Consider

withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function *[see Dosage and Administration (2.1)]*.~~.~~

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

• ~~Risk of fetal/neonatal morbidity and mortality~~ Fetal Toxicity *[see Warnings and Precautions (5.1)]*
• Anaphylactic Reactions and Head and ~~neck angioedema~~Neck Angioedema *[see Warnings and Precautions (5.3)]*

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, peripheral ischemia, syncope, ~~postural hypotension~~tachycardia, vasculitis
Central and Peripheral Nervous System: hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo
Gastrointestinal: anorexia, constipation, ~~dyspepsia,**~~ dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia

6.2 ~~Post-marketing~~ Postmarketing Experience
The following adverse reactions have been identified during postapproval use of either aliskiren or amlodipine. 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~~

Aliskiren: 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, nausea, vomiting

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

Dual Blockade of the Renin-Angiotensin-Aldosterone System (RAAS): The concomitant use of aliskiren with other agents acting on the RAAS 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. Most patients receiving the combination of two drugs that inhibit the renin-angiotensin system do not obtain any additional benefit compared to monotherapy. In general, avoid combined use of aliskiren with ACE inhibitors or ARBs, particularly in patients with CrCl less than 60 mL/min.

Monitor blood pressure, renal function, and electrolytes in patients on aliskiren and other agents that affect the RAAS *[see Warnings and Precautions (5.4, 5.6, 5.8)]*.

The concomitant use of aliskiren with an ARB or an ACEI in diabetic patients is contraindicated (b) (4) *[see Contraindications (4)* (b) (4)

8. Under **CLINICAL PHARMACOLOGY**, **Figure 5** was updated with superscript ** after the words "ramipril, valsartan, and irbesartan" and the words "no dose adjustment" were deleted; the following text was added below the figure:

*Ketoconazole: A 400 mg once daily dose was not studied, but would be expected to increase aliskiren blood levels further.
**Ramipril, valsartan, irbesartan: In general, avoid combined use of aliskiren with ACE inhibitors or ARBs, particularly in patients with CrCl less than 60 mL/min *[see Drug Interactions. [(7)].*

9. Under **CLINICAL PHARMACOLOGY**, **Figure 6** was updated with superscript ** after the words "ramipril, valsartan, and irbesartan" and the words "no dose adjustment" were deleted; the following text was added below the figure:

*Furosemide: Patients receiving furosemide could find its effects diminished after starting aliskiren. In patients with heart failure, coadministration of aliskiren (300 mg/day) reduced plasma AUC and C_{max} 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 coadministered with aliskiren 300 mg/day.
**Ramipril, valsartan, irbesartan: In general, avoid combined use of aliskiren with ACE inhibitors or ARBs, particularly in patients with CrCl less than 60 mL/min *[see Drug Interactions. [(7)].*

10. Under **PATIENT COUNSELING INFORMATION,** the following text was added/deleted:

Advise the patient to read the~~See~~ FDA-a~~A~~pproved p~~P~~atient l~~L~~abeling[AV3]~~Approved Patient Labeling~~ (Patient Information)

~~Healthcare professionals should instruct their patients to read the Patient Package Insert before starting Tekamlo and to reread each time the prescription is renewed. Patients should be instructed to inform their doctor or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.~~

Pregnancy

Inform female~~Female~~ patients of childbearing age ~~should be told~~ about the consequences of exposure to Tekamlo during pregnancy. ~~-~~Discuss treatment options with women planning to become pregnant. Advise patients ~~Patients should be asked~~ to report pregnancies to their physician as soon as possible.

Symptomatic Hypotension

Caution patients receiving Tekamlo that lightheadedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician. Tell patients that if syncope occurs, discontinue Tekamlo until the physician has been consulted.

Caution all patients that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Anaphylactic Reactions and Angioedema

Advise patients~~Patients should be advised and told~~ to ~~report~~ immediately report any signs or symptoms suggesting a severe allergic reaction (difficulty breathing or swallowing, tightness of the chest, hives, general rash, swelling, itching, dizziness, vomiting, or abdominal pain) or angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician. Angioedema, including laryngeal edema, may occur at any time during treatment with Tekamlo.

Potassium Supplements

Tell patients receiving Tekamlo not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician.

Relationship to Meals

Advise patients to~~Patients should~~ establish a routine pattern for taking Tekamlo with regard to meals. High-fat meals decrease absorption substantially.

11. Multiple editorial changes were made in the following sections: 1, 2.1, 4, 5.3, 5.4, 5.7, 6.1, 7, 8.1, 8.5, 8.6, 8.7, 10, 12.1, 12.2, 12.3, 13.1, 14.1, 14.2, and 16,

12. The revision date and version number were updated.

In the Tekamlo PPI:

1. The following revisions were made to the heading:

~~**FDA-Approved Patient Labeling**~~

Patient Information

Tekamlo™ ***(těk'-ăm-lō)***
~~**Tekamlo**~~
(aliskiren and amlodipine)
Tablets

2. The following section was moved from the end of the PPI to the beginning of the PPI:

What is high blood pressure (hypertension)?

Blood pressure is the force of blood in your blood vessels when your heart beats and when your heart rests. You have high blood pressure when the force is too much.

High blood pressure makes the heart work harder to pump blood through the body and causes damage to blood vessels. Tekamlo can help your blood vessels relax so your blood pressure is lower. Medicines that lower your blood pressure may lower your chance of having a stroke or heart attack.

3. Under **Who should not take Tekamlo?**, the following text was added/deleted:

Do not take Tekamlo if you:

- (b) (4) get pregnant, stop taking Tekamlo and call your doctor right away. If you plan to become pregnant, talk to your doctor about other treatment options for your high blood pressure.
- (b) (4) have diabetes and are taking a kind of medicine called an angiotensin receptor blocker (ARB) or angiotensin-converting enzyme inhibitor (ACEI).
- (b) (4) are allergic (hypersensitive) to aliskiren, amlodipine, or other dihydropyridines (calcium-channel blockers, a group of medicines to lower blood pressure to which amlodipine belongs) or any of the other ingredients of Tekamlo listed at the end of this leaflet.

4. Under **Before taking Tekamlo, tell your doctor if you**:, the following text was added to the third bullet:

   - have ever had an allergic reaction to another blood pressure medicine. Symptoms may include: swelling of the face, lips, tongue, throat, arms and legs, and trouble breathing (angioedema).

5. Under **Especially tell your doctor if you take:**, the following text was added:

   - a kind of medicine to control blood pressure called angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACEI)
   - medicines used to lower blood pressure, water pills (also called "diuretics"), especially potassium[AV4] sparing diuretics")
   - medicines for treating fungus or fungal infections (like itraconazole or ketoconazole)
   - cyclosporine (Gengraf®, Neoral, Sandimmune), a medicine used to suppress the immune system
   - potassium-containing medicines, potassium supplements, or salt substitutes containing potassium
   - simvastatin (Zocor®) or atorvastatin (Lipitor®), medicines used to treat high cholesterol®)
   - nonsteroidalnon-steroidal anti-inflammatory drugs (NSAIDs) (like ibuprofen or naproxen), including selective Cyclooxygenase-2 inhibitors (COX-2 inhibitors)
   - medicines used to treat AIDS or HIV infections (such as ritonavir, indinavir)

   Ask your doctor if you are not sure whether you are taking one of the medicines listed above. Know the medicines you take. Keep a list of them to show your doctor or pharmacist when you get a new medicine. Your doctor or pharmacist will know what medicines are safe to take together.Know your medicines.Know your medicines. Keep a list of all your medicines. Show this list to your doctor or pharmacist when you get a new medicine. Your doctor or pharmacist will know what medicines are safe to take together.

6. Under **What are the possible side effects of Tekamlo?**, the following text was added/deleted:

   - • **Harm to an unborn baby, causing injury or death. See "What is the most important information I should know about Tekamlo?"**
   - Severe Allergic Reactions and Angioedema (hypersensitivity).. Aliskiren, one of the medicines in Tekamlo, can cause difficulty breathing or swallowing, tightness of the chest, hives, general rash, swelling, itching, dizziness, vomiting, or abdominal pain (signs of a severe allergic reaction called anaphylactic reactions).). Aliskiren can also

cause swelling of your face, lips, tongue, throat, arms and legs, or the whole body (signs of angioedema). Stop taking Tekamlo and get~~Get~~ medical help right away. Tell ~~and tell~~ your doctor if you get any one or more of these symptoms. Angioedema can happen at any time while you are taking Tekamlo.

- **Low blood pressure (hypotension).** Your blood pressure may get too low if you also take water pills, are on a low-salt diet, get dialysis treatments, have heart problems, or get sick with vomiting or diarrhea. Lie down if you feel faint or get dizzy. Call your doctor right away.
- **Possible increased chest pain or risk of heart attack.** ~~It is rare, but w~~When~~when~~ you first start taking Tekamlo or increase your dose, you may have a heart attack or your angina may get worse. If that happens, call your doctor right away or go directly to a hospital emergency room.
- **Renal impairment or failure.** Aliskiren, one of the medicines in Tekamlo, may cause renal disorder with symptoms such as severely decreased urine output or decreased urine output (signs of renal impairment or failure).

7. Under **Common side effects of Tekamlo include:**, the following text was added:

   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), stomach pain, nausea, flushing (hot or warm feeling in your face), arrhythmia (irregular heartbeat),heart palpitations (very fast heartbeat)

8. 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, 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

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
03/27/2015