DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022545/S-011; S-013

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 Applications (sNDAs) dated and received March 9, 2012 (S-011) and August 1, 2012 (S-013), 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.

These "Prior Approval" supplemental new drug applications 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:

Boxed Warning: Fetal Toxicity	02/2012
Contraindications: Concomitant use with ARBs or ACEIs in diabetes (4)	03/2012
Contraindications: Hypersensitivity (4)	09/2012
Warnings and Precautions: Fetal Toxicity (5.1)	02/2012
Warnings and Precautions (5.2, 5.4, 5.6, 5.8)	03/2012
Warnings and Precautions (5.4, 5.5)	09/2012
Warnings and Precautions (5.3)	09/2012

2. In **HIGHLIGHTS/DOSAGE AND ADMINISTRATION**, the cross references were updated.

3. In **HIGHLIGHTS/CONTRAINDICATIONS**, the following text was added:

   Do not use with angiotensin receptor blockers (ARBs) or ACE inhibitors (ACEIs) in patients with diabetes (4)
   Known hypersensitivity to any component (4)

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

   - Avoid concomitant use with ARBs or ACEI in patients with renal impairment (GFR<60 mL/min) (5.2)
   - Anaphylactic Reactions and Head and Neck Angioedema: Discontinue Tekamlo and monitor until signs and symptoms resolve. (5.3)
   - Hypotension in volume- and/or salt-depleted patients: 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. (5.5)
- Impaired renal function: Monitor serum creatinine periodically. (5.6)
- ~~Patients with hepatic impairment: Titrate slowly. (5.7)~~
- ~~Patients with heart failure: Titrate slowly. (5.8)~~
- Hyperkalemia: Monitor potassium levels periodically. (5.8~~5.10~~)

5. Under **INDICATIONS AND USAGE**, the following text was deleted:

~~*Initial Therapy*~~
~~Use Tekamlo as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals. Base the choice of Tekamlo as initial therapy on an assessment of potential benefits and risks.~~

~~*Add-On Therapy*~~
~~Switch a patient whose blood pressure is not adequately controlled with aliskiren alone or amlodipine besylate (or another dihydropyridine calcium channel blocker) to combination therapy with Tekamlo.~~

~~*Replacement Therapy*~~
~~Tekamlo may be substituted for its titrated components.~~

~~Patients with moderate or severe hypertension are at a relatively high risk for cardiovascular events (such as strokes, heart attacks, and heart failure), kidney failure, and vision problems, so prompt treatment is clinically relevant. Individualize the decision to use a combination as initial therapy by weighing factors such as baseline blood pressure, the target goal, and the incremental likelihood of achieving goal with a combination compared to monotherapy. Individual blood pressure goals may vary based upon the patient's risk.~~

Data from the high-dose multifactorial study *[see Clinical Studies (14)]* provide estimates of the probability of reaching a target blood pressure with Tekamlo compared to aliskiren or amlodipine monotherapy. The figures below provide estimates of the likelihood of achieving systolic or diastolic blood pressure control with Tekamlo 300 mg/10 mg, based upon baseline systolic or diastolic blood pressure. The curve of each treatment group was estimated by logistic regression modeling. The estimated likelihood at the right tail of each curve is less reliable because of a small number of subjects with high baseline blood pressures.

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

2.1 General Considerations
The recommended initial once-daily dose of Tekamlo is 150 mg/5 mg. Titrate as needed to a maximum of 300 mg/10 mg.

The blood pressure lowering effects are largely attained within 1-2 weeks. If blood pressure remains uncontrolled after 2 to 4 weeks of therapy, titrate the dose to a maximum of Tekamlo 300 mg/10 mg once daily.

~~**2.2 Dose Selection**~~

~~The recommended initial once-daily dose of Tekamlo is 150 mg/5 mg. Titrate as needed to a maximum of 300 mg/10 mg.~~

~~**2.3 Dose Titration**~~
~~If blood pressure remains uncontrolled after 2 to 4 weeks of therapy, titrate the dose to a maximum of Tekamlo 300 mg/10 mg once daily.~~

~~**2.4 Initial Therapy**~~
~~The usual recommended starting dose of Tekamlo is 150 mg/5 mg once daily as needed to control blood pressure. Titrate the dose to a maximum of 300 mg/10 mg once daily. Tekamlo is not recommended for use as initial therapy in patients with intravascular volume depletion *[see Warnings and Precautions (5.4)]*.~~

7. Under **DOSAGE AND ADMINISTRATION**, the subsections were re-numbered to reflect the content changes.

8. Under **CONTRAINDICATIONS**, the following text was added/deleted:

   Do not use aliskiren with ARBs or ACEIs in patients with diabetes *[see Warnings and Precautions(5.2), Clinical ~~Trials~~ Studies(14.2)]*.

   Tekamlo is contraindicated in patients with known hypersensitivity to any of the components.

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

   5.3 Anaphylactic Reactions and Head and Neck Angioedema

   Aliskiren
   Hypersensitivity reactions such as anaphylactic reactions and angioedema of the face, extremities, lips, tongue, glottis and/or larynx ~~has~~ have been reported in patients treated with aliskiren and has necessitated hospitalization and intubation. This may occur at any time during treatment and has occurred in patients with and without a history of angioedema with ACE inhibitors or angiotensin receptor antagonists. Anaphylactic reactions have been reported from post-marketing experience with unknown frequency. If angioedema involves the throat, tongue, glottis or larynx, or if the patient has a history of upper respiratory surgery, airway obstruction may occur and be fatal. Patients who experience these effects, even without respiratory distress, require prolonged observation and appropriate monitoring measures, since treatment with antihistamines and corticosteroids may not be sufficient to prevent respiratory involvement. Prompt administration of subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 ml) and measures to ensure a patent airway may be necessary.

   Discontinue Tekamlo immediately in patients who develop anaphylactic reactions or angioedema and do not re-administer.

   5.4 Hypotension
   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 Tekamlo, or start the treatment under close medical supervision.

A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

Amlodipine besylate
Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. Because of the gradual onset of action, acute hypotension is unlikely.

5.5 Risk of Myocardial Infarction or Increased Angina
Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of amlodipine, particularly with severe obstructive coronary artery disease. ~~Rarely, initiation or change to the dose of a calcium channel blocker has resulted in the development of documented increased frequency, duration or severity of angina or acute myocardial infarction, particularly in patients with severe obstructive coronary artery disease. The mechanism of this effect has not been elucidated.~~

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 renin-angiotensin system. Patients whose renal function may depend in part on the activity of the reninangiotensin 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 and Precautions (5.2), Clinical ~~Trials~~ Studies (14.2)]*. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function.

~~**5.7 Patients with Hepatic Impairment**~~

~~*Amlodipine besylate*~~
~~Amlodipine is extensively metabolized by the liver and the plasma elimination half-life is 56 hours in patients with impaired hepatic function, therefore, caution should be exercised when administering Tekamlo to patients with severe hepatic impairment.~~

~~**5.8 Patients with Congestive Heart Failure**~~

~~*Amlodipine besylate*~~
~~Amlodipine (5-10 mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). Amlodipine has been compared to placebo in four 8-12 week studies of patients with NYHA Class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or left ventricular ejection fraction.~~

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

Urinary System: ~~micturation~~micturition frequency, ~~micturation~~micturition disorder, nocturia

11. Under **ADVERSE REACTIONS/Post-marketing Experience,** the following text was added:

Aliskiren: Peripheral edema, severe cutaneous adverse reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis

Hypersensitivity: anaphylactic reactions and angioedema requiring airway management and hospitalization.

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

Amlodipine besylate

~~In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.~~

~~*Cimetidine*: Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.~~
~~*Grapefruit juice*: Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.~~

~~*Maalox® (antacid)*: Co-administration of the antacid Maalox with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.~~

~~*Sildenafil*: A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.~~

~~*Atorvastatin*: Co-administration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady-state pharmacokinetic parameters of atorvastatin.~~

~~*Digoxin*: Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.~~

~~*Ethanol (alcohol)*: Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.~~

~~*Warfarin*: Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.~~

Simvastatin: Co-administration of ~~multiple doses of 10 mg of amlodipine with 80 mg~~ simvastatin with amlodipine ~~resulted in a 77%~~ increases the systemic ~~in~~ exposure of~~to~~ simvastatin ~~compared to simvastatin alone~~. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

CYP3A4 Inhibitors: Co-administration with CYP3A inhibitors (moderate and strong) result in increased systemic exposure to amlodipine warranting dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A4 inhibitors to determine the need for dose adjustment.

CYP3A4 Inducers: No information is available on the quantitative effects of CYP3A4 inducers on amlodipine. Blood pressure should be monitored when amlodipine is co-administered with CYP3A4 inducers.

13. Under **USE IN SPECIFIC POPULATIONS**, the following text was added/deleted:

Amlodipine
No evidence of teratogenicity or embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses up to 10 mg amlodipine/kg/day during their respective periods of major organogenesis. However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold). Amlodipine has been shown to prolong both the gestation period and the duration of labor in rats at this dose. ~~In developmental toxicity studies, pregnant rats and rabbits received oral amlodipine maleate during organogenesis at doses approximately 10 and 20 times the maximum recommended human dose (MRHD) based on body surface area (mg/m2), respectively, in rats and rabbits. (Actual animal doses were up to 10 mg/kg/day.) No evidence of teratogenicity or other embryofetal toxicity was observed. However, litter size was decreased approximately 50% and the number of intrauterine deaths was increased approximately 5-fold for rats receiving amlodipine maleate at doses approximately 10 times the MRHD based on body surface area (mg/m2) for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose.~~

8.5 Geriatric Use

~~*Tekamlo*~~

Exposure to aliskiren and amlodipine is increased in elderly patients, thus consider lower initial doses of Tekamlo *[see Clinical Pharmacology (12.3)].*
In the short-term controlled clinical trials of Tekamlo, 17% of patients treated with Tekamlo were ≥65 years. 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.

~~*Aliskiren*~~
~~Impact of aging on aliskiren pharmacokinetics has been assessed, when compared to young adults (18-40 years), aliskiren mean AUC and Cmax in elderly subjects (> 65 years) are increased by 57% and 28%, respectively. However, differences in efficacy and~~

~~safety between the elderly and younger populations were minor, indicating that differences in exposure due to age do not significantly alter the clinical effect of the drug. Therefore, no starting dose adjustment in geriatric population is required.~~

~~*Amlodipine*~~
~~Other reported clinical experience has not identified differences in responses between the elderly and younger patients. However, elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40-60%. In general dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.~~

8.6 Hepatic Impairment

Exposure to amlodipine is increased in patients with hepatic insufficiency, thus consider using lower doses of Tekamlo *[see Clinical Pharmacology (12.3)]*.

8.6 Renal impairment

There is no impact of renal function on the pharmacokinetics of aliskiren and amlodipine. However, safety and effectiveness of Tekamlo in patients with severe renal impairment (creatinine clearance ~~CrCL~~ <30 mL/min) have not been established as these patients ~~with eGFR <30ml/min~~ were excluded in clinical trials *[see Warnings and Precautions (5.6), Clinical Pharmacology (12.3) and Clinical ~~Trials~~ Studies (14)]*.

14. Under **OVERDOSAGE**, the following text was added/deleted:

Aliskiren
Limited data are available related to overdosage in humans. The most likely manifestation of overdosage would be hypotension. If symptomatic hypotension should occur, provide supportive treatment. Aliskiren is poorly dialyzed. Therefore, hemodialysis is not adequate to treat aliskiren overexposure *[see Clinical Pharmacology (12.3)]*.

Amlodipine besylate
~~Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg or higher in dogs (11 or more times the maximum recommended human dose on a mg/m2 basis) caused a marked peripheral vasodilation and hypotension~~. Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported. In humans, experience with intentional overdosage of amlodipine is limited. ~~Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) was hospitalized, underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A case of accidental drug overdose has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart~~

~~rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted.~~

Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg or higher in dogs (11 or more times the maximum recommended human dose on a mg/m2 basis) caused a marked peripheral vasodilation and hypotension.

If massive overdose should occur, initiate active cardiac and respiratory monitoring ~~should be instituted~~. Frequent blood pressure measurements are essential. Should hypotension occur, provide cardiovascular support including elevation of the extremities and the judicious administration of fluids ~~should be initiated~~. If hypotension remains unresponsive to these conservative measures, consider administration of vasopressors (such as phenylephrine) ~~should be considered~~ with attention to circulating volume and urine output. I~~ntravenous calcium gluconate may help to reverse the effects of calcium entry blockade.~~ As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption.

15. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics**, the following text was added/deleted:

Amlodipine besylate
Peak plasma concentrations of amlodipine are reached 6-12 hours after an oral administration of amlodipine. Absolute bioavailability has been estimated to be between 64% and 90%. The bioavailability of amlodipine is not altered by the presence of food. ~~Steady state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.~~

The apparent volume of distribution of amlodipine is about 21 L/kg. Approximately 93% of circulating amlodipine is bound to plasma proteins in hypertensive patients.

Amlodipine besylate
Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine. Elimination of amlodipine from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours. Steady state plasma levels are reached after once-daily dosing for 7-8 days.

Drug interactions:

Aliskiren exposure is increased slightly (AUC increased 29%) when aliskiren is co-administered with amlodipine, while amlodipine exposure remains unchanged when co-administered with aliskiren. The slight exposure increase of aliskiren in the presence of amlodipine is not clinically relevant.

In vitro data in human plasma indicate that amlodipine has no effect on the protein binding of digoxin, phenytoin, warfarin, and indomethacin.

Cimetidine: Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

Grapefruit juice: Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

Maalox® (antacid): Co-administration of the antacid Maalox with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil: A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Atorvastatin: Co-administration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady-state pharmacokinetic parameters of atorvastatin.

Digoxin: Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

Ethanol (alcohol): Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.

Warfarin: Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

Simvastatin: Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone.

CYP3A inhibitors: Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers did not significantly change amlodipine systemic exposure. However, strong inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent.

Special Populations

Pediatric Patients
The pharmacokinetics of Tekamlo have not been investigated in patients <18 years of age.

Geriatric Patients
Impact of aging on aliskiren pharmacokinetics has been assessed. When compared to young adults (18-40 years), aliskiren mean AUC and C_{max} in elderly subjects (> 65 years) are increased by 57% and 28%, respectively. In the elderly, clearance of amlodipine is

decreased with resulting increases in peak plasma levels, elimination half-life and area-under-the-plasma-concentration curve. ~~The pharmacokinetics of aliskiren were studied in the elderly (□65 years). Exposure (measured by AUC) is increased in elderly patients. Adjustment of the starting dose is not required in these patients. Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40%-60%; therefore, a lower initial dose of amlodipine may be required.~~

Race
With Tekamlo, pharmacokinetic differences due to race have not been studied. The pharmacokinetic differences among Blacks, Caucasians, and Japanese are minimal with aliskiren therapy.

Hepatic Impairment

The pharmacokinetics of aliskiren is not significantly affected in patients with mild-to-severe liver disease. Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40%-60% *[see Use in Specific Populations (8.6)]*.

Renal Impairment
~~*Aliskiren*~~
The pharmacokinetics of aliskiren was evaluated in patients with varying degrees of renal impairment. Rate and extent of exposure (AUC and Cmax) of aliskiren in subjects with renal impairment did not show a consistent correlation with the severity of renal impairment. ~~Adjustment of the starting dose is not required in these patients *[see Warnings and Precautions (5.6)]*.~~

The pharmacokinetics of aliskiren following administration of a single oral dose of 300 mg was evaluated in patients with End Stage Renal Disease (ESRD) undergoing hemodialysis. When compared to ~~matched~~ healthy subjects, changes in the rate and extent of aliskiren exposure (Cmax and AUC) in ESRD patients undergoing hemodialysis was not clinically significant. Timing of hemodialysis did not significantly alter the pharmacokinetics of aliskiren in ESRD patients. ~~Therefore, no dose adjustment is warranted in ESRD patients receiving hemodialysis.~~

~~*Amlodipine besylate*~~
The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. ~~Patients with renal failure may therefore receive the usual initial dose~~ *[see Warnings and Precautions (5.6) and Use in Specific Populations (8.7)]*.

~~*Hepatic Impairment*~~

~~*Aliskiren*~~
~~The pharmacokinetics of aliskiren were not significantly affected in patients with mild-to-severe liver disease. Consequently, adjustment of the starting dose is not required in these patients *[see Warnings and Precautions (5.7)]*.~~

~~*Amlodipine besylate*~~

~~Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40%-60%; therefore, a lower initial dose of amlodipine may be required *[see Warnings and Precautions (5.7)]*.~~

~~*Drug Interactions*~~
~~Aliskiren exposure is increased slightly (AUC increased 29%) when aliskiren is co-administered with amlodipine, while amlodipine exposure remains unchanged when co-administered with aliskiren. The slight exposure increase of aliskiren in the presence of amlodipine is not clinically relevant~~.

16. Under **NONCLINICAL TOXICOLOGY**, the following text was added/deleted:

Studies with Amlodipine besylate
Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg amlodipine/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on mg/m2 basis, similar to the maximum recommended human dose (MRHD) of 10 mg amlodipine/day. For the rat, the highest dose was, on a mg/m2 basis, about ~~two and a half times~~ twice the MRHD. ~~(Calculations based on a 60 kg patient.)~~ Mutagenicity studies conducted with amlodipine maleate revealed no drug-related effects at either the gene or chromosome level. There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses of up to 10 mg amlodipine/kg/day (about ~~10~~8 times the MRHD of 10 mg/day on a mg/m2 basis).

17. Under **PATIENT COUNSELING INFORMATION**, the following text was added:

Anaphylactic Reactions and Angioedema

Patients should be advised and told to report immediately 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.

18. In the **FDA-Approved Patient Labeling,** under **What should I tell my doctor before taking Tekamlo?**, the following bullet was added:

- suffer from heart disorders or if you experienced a heart attack

19. In the **FDA-Approved Patient Labeling,** under **Especially tell your doctor if you take:**, the following bullets were added:

- simvastatin (Zocor®) or atorvastatin (Lipitor®)
- medicines used to treat AIDS or HIV infections (such as ritonavir, indinavir)

20. In the **FDA-Approved Patient Labeling,** under **What are the possible side effects of Tekamlo?**, the following text was added/deleted:

    - **Severe Allergic Reactions and Angioedema**: 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). Aliskiren can also cause swelling of your face, lips, tongue, throat, arms and legs, or the whole body (signs of angioedema). Get medical help right away and tell your doctor if you get any one or more of these symptoms. ~~Serious allergic reactions~~Angioedema can happen at any time while you are taking Tekamlo.

21. 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 these supplemental applications, and they are 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:
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/s/

MARY R SOUTHWORTH
09/28/2012