DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022107/S-025

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 Tekturna HCT (aliskiren/hydrochlorothiazide) 150/12.5 mg, 150/25 mg, 300/12.5 mg, and 300/25 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 cross reference was updated:

   Warnings and Precautions (5.1, 5.2, 5.95, 5.8) 02/2015

2. Under **HIGHLIGHTS/DOSAGE AND ADMINITRATION**, the following text was added/deleted:

   - Initiate~~The antihypertensive effect is largely manifested within 1 week,~~ with 150/12.5mg daily. Titrate as needed~~maximal effects seen at around 4 weeks. If blood pressure remains uncontrolled after 2 to 4 weeks of therapy, titrate~~ up to a maximum of 300/25 mg~~.~~ (2.2)
   - Order of increasing mean effect: 150/12.5 mg, 150/25 mg or 300/12.5 mg, and 300/25 mg (2.1)
   - One tablet daily, with a routine pattern with regard to meals. (2.7)
   - Add-on or Initial therapy: Initiate with 150/12.5mg. Titrate as needed up to a maximum of 300/25 mg. (2.3, 2.5)
   - Replacement therapy: May be substituted for titrated components (2.4)

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

   Do not use with angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme~~ACE~~ inhibitors (ACEIs) in patients with diabetes. (4)
   Anuria (4)
   Hypersensitivity to sulfonamide derived drugs or to any of the components. (4)

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

   - Avoid concomitant use with ARBs or ACEIs particularly in patients with renal impairment [creatinine clearance (CrCl) ~~(GFR~~<60 mL/min].~~)~~ (5.2, 5.4)~~)~~

- Anaphylactic Reactions and ~~Head and Neck~~ Angioedema.~~: Discontinue Tekturna HCT and monitor until signs and symptoms resolve.~~ (5.3)
- Hypotension: ~~c~~Correct imbalances ~~-~~in volume and/or salt~~-~~depleted patients.~~-~~ [redacted] (5.4)
- Impaired Renal Function~~renal function~~: Monitor serum creatinine periodically. (5.5)
- Hypersensitivity Reactions: May occur from HCTZ component (5.6)
- Hyperkalemia: Monitor potassium levels periodically. (5.9)
- Acute Myopia and Secondary Angle Closure Glaucoma. (5.1~~2~~1)
- [redacted]
- ~~Hydrochlorothiazide has been associated with acute angle-closure glaucoma (5.11)~~

5. In **HIGHIGHTS/DRUG INTERACTIONS**, the following text was added/deleted:

Cyclosporine or Itraconazole: Avoid concomitant use. (5.10, ~~-~~7, 12.3)

[redacted]

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

- Antidiabetic Drugs: Dosage adjustment of antidiabetic may be required. (7)
- Cholestyramine and Colestipol: Reduced absorption of thiazides. (7)
- Lithium: Increased~~sIncreased~~ risk of [redacted]-lithium toxicity when used with diuretics. (~~5.8, Monitor serum lithium concentrations during concurrent use.~~ (7)

6. Under **DOSAGE AND ADMINISTRATION**, the following section was deleted and the remaining section was re-numbered:

~~**2.6 Use with Other Antihypertensive Drugs**~~

~~Tekturna HCT 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 a glomerular filtration rate (GFR) less than 60 mL/min [see Warnings and Precautions (5.2)]. There are no data available with use of Tekturna HCT with angiotensin-converting enzyme inhibitors (ACEIs) or beta-blockers (BB) [see Clinical Studies (14)].~~

7. 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) and~~,~~ Clinical Studies (14.4)]*.

~~Because of the hydrochlorothiazide component,~~ Tekturna HCT is contraindicated in patients with anuria or hypersensitivity to sulfonamide-derived drugs like HCTZ or to any of the components *[see Warnings and Precautions (5.6) and Adverse Reactions (6.1)]*. Hypersensitivity reactions may range from urticaria to anaphylaxis ~~*[see Adverse Reactions (6.1)].*~~

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

5.2 Renal Impairment/Hyperkalemia/Hypotension when Tekturna HCT is Given in Combination with ARBs or ACEIs

Tekturna HCT 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~~Tekturna HCT~~ with ACE~~s~~ inhibitors or ARBs, particularly in

patients with moderate renal impairment (GFR ~~<60 ml/min).~~less than 60 mL/min) (b) (4) (b) (4) *, Contraindications (4), Drug Interactions (7), and Clinical Studies 14.3].*

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

5.5 Impaired Renal Function

Monitor renal function periodically in patients treated with Tekturna HCT. Changes in renal function, including acute renal failure, can be caused by drugs that affect the ~~renin-angiotensin-aldosterone system~~RAAS and by diuretics. Patients whose renal function may depend in part on the activity of the ~~renin-angiotensin-aldosterone system~~RAAS (e.g., patients with renal artery stenosis, severe heart failure, post-myocardial infarction or volume depletion) or patients receiving ARB, ACEI or ~~non-steroidal~~nonsteroidal anti-inflammatory ~~(NSAID)~~drug (NSAID) , including selective Cyclooxygenase-2 inhibitors (COX-2 inhibitors), therapy may be at particular risk of developing acute renal failure on Tekturna HCT *[see ~~Contraindications (4)~~, Warnings and Precautions (5.2), Drug Interactions (7), and Clinical Studies (14.4)]*. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on Tekturna HCT.

5.6 Hypersensitivity Reactions

Hydrochlorothiazide (HCTZ)

Hypersensitivity reactions to HCTZ~~hydrochlorothiazide~~ may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

5.7 Systemic Lupus Erythematosus

Hydrochlorothiazide (HCTZ)

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

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

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- ~~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)]*.
- Hypotension ~~in volume- and/or salt-depleted patients~~ *[see Warnings and Precautions (5.4)].*

Clinical Laboratory Test Abnormalities

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely ~~associated with administration of Tekturna HCT in patients with hypertension not concomitantly treated with an ARB or ACEI.~~associated with administration of Tekturna HCT in patients with hypertension not concomitantly treated with an ARB or ACEI.

6.2 Post-Marketing Experience

Aliskiren

Hypersensitivity: anaphylactic reactions and angioedema requiring airway management and hospitalization, urticaria, peripheral edema, hepatic enzyme increase with clinical symptoms of hepatic dysfunction, severe cutaneous adverse reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, pruritus, erythema, nausea, vomiting

(b) (4)
~~Peripheral edema~~
(b) (4)
~~Severe cutaneous adverse reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis~~
(b) (4)

Hydrochlorothiazide

Acute renal failure, renal disorder, aplastic anemia, erythema mutliforme, pyrexia, muscle spasm, asthenia, acute angle-closure glaucoma, b*one marrow failure*, *worsening of diabetes control, hypokalemia, blood lipids increased, hyponatremia, hypomagnesemia, hypercalcemia, hyperchloremic alkalosis*, *impotence*, *visual impairment*

Pathological changes in the parathyroid gland of patients with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. If hypercalcemia occurs, further diagnostic evaluation is necessary.

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

Cyclosporine: Avoid coadministration~~co-administration~~ of cyclosporine with aliskiren *[see Warnings and Precautions (5.10) and Clinical Pharmacology (12.3)]*.~~.~~

Itraconazole: Avoid coadministration~~co-administration~~ of itraconazole with aliskiren *[see Warnings and Precautions (5.7) and~~See~~ Clinical Pharmacology (12.3)]*.

Nonsteroidal~~Non-Steroidal~~ Anti-Inflammatory Drugs~~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, coadministration~~co-administration~~ of NSAIDs, including selective COX-2 inhibitors with agents that affect the RAAS~~renin-angiotensin-aldosterone 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 aliskiren may be attenuated by NSAIDs.

Dual Blockade of the Renin-Angiotensin-Aldosterone System (RAAS):~~renin~~ (b) (4) The concomitant use of aliskiren with other agents acting on the (b) (4) 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 [A1]~~Monitor~~ blood pressure, renal function, and electrolytes in patients on aliskiren and other agents that affect the RAAS (b) (4) *[see Warnings and Precautions (5.4, 5.5, 5.9)]*.

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

Furosemide: Oral coadministration~~co-administration~~ of aliskiren and furosemide reduced exposure to furosemide. Monitor diuretic effects when furosemide is coadministered~~co-administered~~ with aliskiren.

Hydrochlorothiazide (HCTZ)

When administered concurrently, the following drugs may interact with thiazide diuretics.

Antidiabetic drugs (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be required.

~~*Lithium:* Lithium:~~ Diuretic agents increase[A3] the risk of lithium toxicity. Increases in serum~~Refer to the package insert for~~ lithium concentrations and lithium toxicity have been reported during concomitant administration~~before use~~ of lithium~~such preparation~~ with angiotensin II receptor antagonists.~~Tekturna HCT.~~ Monitoring of serum lithium levels ~~concentrations~~ is recommended during concomitant~~concurrent~~ use.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and COX-2 selective agents[A4]~~*anti-inflammatory drugs:*~~ When Tekturna HCT and NSAIDs~~nonsteroidal anti-inflammatory agents~~ are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Ion-exchange Resins~~resins~~: Staggering the dosage of HCTZ~~hydrochlorothiazide~~ and ion exchange resins (e.g., cholestyramine, colestipol) such that HCTZ~~hydrochlorothiazide~~ is administered at least 4 hours before or 4 to 6 hours after the administration of resins would potentially minimize the interaction *[see Clinical Pharmacology (12.3)]*.

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

8.6 Renal Impairment

Safety and effectiveness of Tekturna HCT in patients with severe renal impairment [creatinine clearance (CrCl) less than ~~or equal to ≤~~ 30 mL/min]~~)~~ have not been established *[see Warnings and Precautions (5.6), Clinical Pharmacology (12.3) and Clinical Studies (14)]*. ~~No dose adjustment is required in patients with mild (CrCl 60-90 mL/min) or moderate (CrCl 30-60) renal impairment.~~

No dose adjustment is required in patients with mild (CrCl 60 to 90 mL/min) or moderate (CrCl 30 to 60 mL/min) renal impairment.

12. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics**, figures 5 and 6 were updated:

Figure 5 was updated to include the superscript ** after Ramipril, valsartan, and irbesartan. The text "no dose adjustment" was deleted. The following text was added below Figure 5:
*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)]

Figure 6 was updated to include the superscript ** after Ramipril, valsartan, and irbesartan. The text "no dose adjustment" was deleted. The following text was added below Figure 6:
*Furosemide: Patients receiving furosemide could find its effects diminished after starting aliskiren.

**Ramipril, valsartan: 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)]

13. Under **CLINICAL STUDIES/Aliskiren in Combination with Other Antihypertensives**, the following text was added/deleted:

Valsartan

Aliskiren 150 mg and 300 mg and valsartan 160 mg and 320 mg were studied alone and in combination in an 8-week, 1,797-patient, randomized, double-blind, placebo-controlled, parallel-group, 4-arm, dose-escalation study. The dosages of aliskiren and valsartan were

started at 150 mg and 160 mg, respectively, and increased at 4~~four~~ weeks to 300 mg and 320 mg, respectively. Seated trough cuff blood pressure was measured at baseline, 4, and 8 weeks. Blood pressure reductions with the combinations were greater than the reductions with the monotherapies as shown in Table 3. In general, avoid use of aliskiren in combination with other drugs that affect the RAAS *[see Contraindications (4), Warnings and Precautions (5), and Drug Interactions (7)]*.

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

Advise the patient to read the~~See~~ FDA-approved patient labeling (Patient Information [A5]).~~)~~ ~~Healthcare professionals should instruct their patients to read the Patient Package Insert before starting Tekturna HCT 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 Tekturna HCT during pregnancy. Discuss treatment options with women planning to become pregnant. Advise patients~~Patients should be asked~~ to report pregnancies to their physicians as soon as possible.

Symptomatic Hypotension

Inform patients ~~A patient receiving Tekturna HCT should be cautioned~~ that lightheadedness can occur, especially during the first days of Tekturna HCT therapy, and that it should be reported to the prescribing physician. Advise~~The~~ patients ~~should be told~~ that if syncope occurs, Tekturna HCT should be discontinued until the physician has been consulted.

Caution~~All~~ patients ~~should be cautioned~~ 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 Tekturna HCT.

Potassium Supplements

Advise patients~~A patient~~ receiving Tekturna HCT ~~should be told~~ not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician.

Relationship to Meals

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

15. Editorial changes were made in the following sections: 1, 2.2, 2.5, 5.1, 5.2, 5.3, 5.4, 5.6, 5.9, 5.11, 5.12, 6.1, 7, 8.1, 8.5, 8.7, 10, 11, 12.1, 12.2, 12.3, 13.1, 14.1, 14.2, 14.4,

16. The revision date and version number were updated.

In The Tekturna HCT PPI:

1. The following changes were made to the heading:

FDA-Approved Patient Labeling

Patient Information

Tekturna® HCT® (tek-turn-a HCT)
(aliskiren and hydrochlorothiazide)
~~, USP)~~
~~Combination~~ Tablets

2. Under **What is high blood pressure?**, the following text was added/deleted:

~~Blood pressure is the force that pushes the blood through~~of blood in your blood vessels when your heart beats and when your heart rests.~~to all the organs of your body~~. You have high blood pressure when the force ~~of your blood moving through your blood vessels~~ is too ~~great~~much. ~~One cause of high blood pressure is renin, a chemical in the body that starts a process that makes blood vessels narrow, leading to high blood pressure.~~
Tekturna HCT reduces high blood pressure.~~ Medicines that lower your blood pressure lower your chance of having a stroke or heart attack.~~ High blood pressure makes the heart work harder to pump blood throughout the body and causes damage to ~~the~~ blood vessels. Tekturna HCT 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.~~If high blood pressure is not treated, it can lead to stroke, heart attack, heart failure, kidney failure, and vision problems~~.

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

Do not take Tekturna HCT if you:

- ~~If you~~ get pregnant, stop taking Tekturna HCT 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
- ~~If you~~ have diabetes and are taking a kind of medicine called an a~~ngiotensin receptor~~ angiotensin receptor blocker (ARB) or angiotensin-converting- enzyme- inhibitor (ACEI).
- ~~Do not take Tekturna HCT if you~~ make very little or no urine due to kidney problems.
- ~~Do not take Tekturna HCT if you~~ are allergic to aliskiren, hydrochlorothiazide, sulfonamides or any of ~~its~~the other ingredients.~~ See~~ of Tekturna HCT listed at the end of this leaflet ~~for a complete list of the ingredients in Tekturna HCT~~.

4. Under **What should I tell my doctor before taking Tekturna HCT?,** the following text was added/deleted:

Before taking Tekturna HCT, tell your doctor if you~~Tell your doctor about all your medical conditions, including whether you~~:

- have kidney problems
- are pregnant or planning to become pregnant. **See "What is the most important information I should know about Tekturna HCT?"**
- have any allergies or asthma
- have liver problems
- have systemic lupus erythematosus (SLE). Tekturna HCT can make your SLE active or worse.
- have ever had an allergic~~a~~ reaction called angioedema, to another blood pressure~~an ACE inhibitor~~ medicine. Symptoms may include~~Angioedema causes~~ swelling of the face, lips, tongue, throat,~~-~~arms, and legs, and may cause difficulty breathing (angioedema).~~-~~

- are breastfeeding. ~~breast feeding.~~ It ~~s~~is not known if Tekturna -HCT passes into your breast milk and of it can harm your baby.

  have any other medical problems

- [redacted] (b) (4)

~~**Tell your doctor about all the medicines you take**~~ including prescription and nonprescription medicines, vitamins and herbal supplements. Tekturna HCT and certain other medicines may affect each other and cause side effects.~~Especially tell your doctor if you are taking:~~

Especially tell your doctor if you are taking:

- a kind of medicine to control blood pressure called angiotensin receptor blocker (ARB) or angiotensin--converting enzyme inhibitor (ACEI)
- cholesterol lowering medicines
  - simvastatin (Zocor®) or atorvastatin (Lipitor®)
  - cholestyramine (Questran, Questran Light, Cholestyramine Light, Locholest Light, Locholest, Prevalite)
  - colestipol (Colestipol hydrochloride, Colestid, Flavored Colestid)

~~medicines usedmedicine~~ to lower ~~cholesterol in your~~ blood pressure ,~~)~~

- water pills (also called "diuretics"), especially potassium--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

~~cholestyramine (for example; Questran, Questran Light, Cholestyramine Light, Locholest Light, Locholest, Prevalite) (~~medicines used~~to lower the cholesterol in your blood)~~

~~colestipol (for example; Colestipol hydrochloride, Colestid, Flavored Colestid) (medicines to lower the cholesterol in your blood)~~

- medicine~~s~~ to treat diabetes, including insulin
- lithium, a medicine used in some types of depression. ~~Do not take Tekturna HCT if you are taking lithium.~~
- medicines used to relieve pain or inflammation, especially nonsteroidal~~Nonsteroidal~~ anti-inflammatory drugs (NSAIDs) (like ibuprofen or naproxen), including selective Cyclooxygenase-2-inhibitors (COX-2 inhibitors) ~~medicines.~~ Ask your doctor if you are not sure if you are taking one of these medicines.

~~blood thinners~~

~~barbiturate or narcotic medicines.~~ Ask your doctor if you are not sure whether~~if~~ 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 ~~these medicines.~~

Your doctor or pharmacist will know what medicines are safe to take together. ~~Know your medicines. Keep a list of your medicines and show it to your doctor or pharmacist when you get a new medicine.~~

5. A new section was added:

What should I avoid while taking Tekturna HCT?
Drinking alcohol. Drinking alcohol during treatment with Amturnide can cause you to have low blood pressure. **See "What are the possible side effects of Tekturna HCT?"**

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

~~1.~~• **Harm~~Injury or death~~ to an unborn baby, causing injury or death. See "What is the most important information I should know about Tekturna HCT?"**

~~2. **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. Drinking alcohol and taking certain medicines (barbiturates or narcotics) can cause low blood pressure to get worse. Lie down if you feel faint or dizzy, and call your doctor right away.~~

• **Severe Allergic Reactions and Angioedema (hypersensitivity).~~.~~** Aliskiren, one of the medicines in Tekturna HCT, 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 reaction).~~)~~. Aliskiren can also cause swelling of the face, lips, tongue, throat, arms and legs, or the whole body (signs of angioedema). Stop taking Tekturna HCT 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 Tekturna HCT.

• **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. Drinking alcohol and taking certain medicines (barbiturates or narcotics) can cause low blood pressure to get worse. Lie down if you feel faint or dizzy, and call your doctor right away.

~~3.~~• **Renal Impairment~~impairment~~ or Failure~~failure~~**. Aliskiren, one of the medicines in Tekturna HCT, may cause renal disorder with symptoms such as severely decreased urine output or decreased urine output (signs of renal impairment or failure).

• **Tekturna HCT may affect your potassium levels.** Your doctor will do blood tests to check your potassium levels.

• **Allergic reactions:** Hydrochlorothiazide, one of the medicines in Amturnide, can cause allergic reactions.

~~4.~~• **Active or Worsened~~worsened~~ Systemic Lupus Erythematosus (SLE).** If you have SLE, tell your doctor right away if you get any new or worse symptoms. Possible signs of SLE are facial rash, joint pain, muscle disorder, fever.

~~5.~~• **Eye problems**. One of the medicines in Tekturna HCT can cause eye problems that may lead to vision loss. Symptoms of eye problems can happen within hours to weeks of starting Tekturna HCT. Tell your doctor right away if you have:
  - Decrease in vision
  - Eye pain

Common side effects of Tekturna HCT include:
- dizziness
- flu-like symptoms
- diarrhea
- cough
- tiredness
- high levels of potassium in the blood (hyperkalemia)
- vertigo
- arthralgia

Less common side effects include skin 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).
Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of Tekturna HCT. For a complete list of side effects, ask your doctor or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1 800 FDA 1088.

7. The following text was deleted from the end of the PPI and repositioned above:

   ~~**Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.**~~

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
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Sincerely,

{See appended electronic signature page}

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/s/

MARY R SOUTHWORTH
03/27/2015