



NDA 022107/S-016

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Lily Chan, PharmD
Director, Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Chan:

Please refer to your Supplemental New Drug Application (sNDA) dated July 7, 2011, and received July 8, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tekturna HCT (aliskiren/hydrochlorothiazide) 150/12.5 mg, 150/250mg, 300/12.5 mg, and 300/25 mg Tablets.

We acknowledge receipt of your submission dated, October 26, 2012.

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~~):

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

----- RECENT MAJOR CHANGES -----	
Boxed Warning: Fetal Toxicity	02/2012
Indications and Usage: Benefits of lowering blood pressure (1)	10/2011
Warnings and Precautions (5.1)	02/2012
Warnings and Precautions (5.11, 5.12)	02/2011

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

- WARNINGS AND PRECAUTIONS**-----
- Head and Neck Angioedema: Discontinue Tekturna HCT and monitor until signs and symptoms resolve. (5.2)
 - Hypotension: ~~in Volume or Salt Depleted Patients:~~ Correct imbalances before volume depletion prior to initiation ~~initiating therapy with Tekturna HCT.~~ (5.3)
 - ~~Patients with Severe Renal Impairment: Not recommended if GFR <30 mL/min~~
Monitor renal function in susceptible patients. (5.4)
 - ~~Patients with Hepatic Impairment: Titrate slowly.~~ (5.5)
 - Hypersensitivity Reactions: May occur from HCTZ component (5.6)
 - Hydrochlorothiazide has been associated with acute angle-closure glaucoma (5.10~~2~~)

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

-----**DRUG INTERACTIONS**-----

Aliskiren:

- Cyclosporine: Avoid concomitant use (7, 12.3)
- Itraconazole: Avoid concomitant use (7, 12.3)

Hydrochlorothiazide:

- ~~Alcohol, Barbiturates, Narcotics: Potentiation of orthostatic hypotension~~
- ~~Corticosteroids, ACTH: Hypokalemia, electrolyte depletion~~
- NSAIDs: ~~Can reduce diuretic, natriuretic, and antihypertensive effects of diuretics. Observe patient closely. Use may lead to 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: ~~Reduced renal clearance and high~~ Increased risk of lithium toxicity when used with diuretics. ~~Should not be given with diuretics. Monitor serum lithium concentrations during concurrent use. (7)~~

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

2.8 Dosing in Specific Populations

Renal Impairment

~~The usual regimens of Tekturna HCT may be followed as long as the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so Tekturna HCT is not recommended.~~ Hepatic Impairment

~~Adjustment of the starting dose is not necessary with hepatic impairment.~~

Hepatic Impairment

~~Adjustment of the starting dose is not necessary with hepatic impairment.~~

Elderly Patients

~~Adjustment of the starting dose is not required for elderly patients.~~

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

5.4 Patients with Severe Renal Impairment Impaired Renal Function

Tekturna HCT

~~In patients with severe renal impairment (GFR <30 mL/min), loop diuretics are preferred to thiazides, so Tekturna HCT is not recommended.~~

Hydrochlorothiazide

~~Uptitrate slowly; in patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.~~

Changes in renal function including acute renal failure can be caused by drugs that inhibit the renin-angiotensin system and by diuretics. Patients whose renal function may depend

in part on the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing acute renal failure on Tekturna HCT. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on Tekturna HCT.

6. Under **WARNINGS AND PRECAUTIONS**, the following section was ~~deleted~~:

~~5.5 Patients with Hepatic Impairment~~

~~Hydrochlorothiazide~~

~~Uptitrate slowly; minor alterations of fluid and electrolyte balance may precipitate hepatic coma.~~

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

5.9 Serum Electrolyte Abnormalities

Tekturna HCT

In the short-term controlled trials of various doses of Tekturna HCT the incidence of hypertensive patients who developed hypokalemia (serum potassium <3.5 mEq/L) was 2.2%; the incidence of hyperkalemia (serum potassium >5.5 mEq/L) was 0.8%. No patients discontinued due to increase or decrease of serum potassium.

~~Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. The intervals should be based on the history of electrolyte abnormalities in patients with aliskiren or hydrochlorothiazide monotherapy. Based on experience with the use of other substances that affect the renin-angiotensin system (RAS), concomitant use of Tekturna HCT with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other drugs that increase potassium levels may lead to increases in serum potassium.~~

Hydrochlorothiazide can cause hypokalemia and hyponatremia. Hypomagnesemia can result in hypokalemia which appears difficult to treat despite potassium repletion. Drugs that inhibit the renin-angiotensin system can cause hyperkalemia. Monitor serum electrolytes periodically.

Hydrochlorothiazide

If hypokalemia is accompanied by clinical signs (e.g., muscular weakness, paresis, or ECG alterations), Tekturna HCT should be discontinued. Correction of hypokalemia and any coexisting hypomagnesaemia is recommended prior to the initiation of thiazides.

8. Under **WARNINGS AND PRECAUTIONS**, the following section was ~~deleted~~:

~~5.10 Renal Artery Stenosis~~

~~No data are available on the use of Tekturna HCT in patients with unilateral or bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.~~

9. Under **WARNINGS AND PRECAUTIONS**, a new section was added:

5.11 Metabolic Disturbances

Hydrochlorothiazide

Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides.

Hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricemia and precipitate gout in susceptible patients.

Hydrochlorothiazide decreases urinary calcium excretion and may cause elevations of serum calcium. Monitor calcium levels in patients with hypercalcemia receiving Tekturna HCT.

10. Under **ADVERSE REACTIONS/Post Marketing Experience**, the section was changed as follows:

6.2 Post-Marketing Experience

The following adverse reactions have been reported in aliskiren post-marketing experience. 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.

Aliskiren

Hypersensitivity: angioedema requiring airway management and hospitalization

Peripheral edema

Blood creatinine increased

Severe cutaneous adverse reactions, including Stevens Johnson syndrome and toxic epidermal necrolysis

Hydrochlorothiazide

Acute renal failure, renal disorder, aplastic anemia, erythema multiforme, pyrexia, muscle spasm, asthenia, acute angle-closure glaucoma, bone 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.*

11. Under **DRUG INTERACTIONS**, the following was added/~~deleted~~:

Aliskiren

Cyclosporine: Avoid co-administration of cyclosporine with aliskiren.

Itraconazole: Avoid co-administration of itraconazole with aliskiren.

Non-Steroidal Anti-Inflammatory Agents (NSAIDs) including Selective Cyclooxygenase 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 COX-2 inhibitors with agents 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.

Hydrochlorothiazide

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

~~*Alcohol, barbiturates, or narcotics*~~: Potentiation of orthostatic hypotension may occur.

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

~~*Other antihypertensive drugs*~~: Additive effect or potentiation.

~~*Cholestyramine and colestipol resins*~~: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively.

~~*Corticosteroids, ACTH*~~: Intensified electrolyte depletion, particularly hypokalemia.

~~*Pressor amines (e.g., norepinephrine)*~~: Possible decreased response to pressor amines but not sufficient to preclude their use.

~~*Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)*~~: Possible increased responsiveness to the muscle relaxants.

~~*Lithium*~~: Should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and increase the risk of lithium toxicity. Refer to the package insert for lithium before use of such preparation with Tekturna HCT. Diuretic agents increase the risk of lithium toxicity. Refer to the package insert for lithium before use of such preparation with Tekturna HCT. Monitoring of serum lithium concentrations is recommended during concurrent use.

~~*Nonsteroidal anti-inflammatory drugs*~~: In some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, When Tekturna HCT and 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: Staggering the dosage of hydrochlorothiazide and ion exchange resins (e.g., cholestyramine, colestipol) such that hydrochlorothiazide is administered at least 4 hours before or 4-6 hours after the administration of resins would potentially minimize the interaction. [See Clinical Pharmacology (12.3)]

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

Hydrochlorothiazide

Thiazides can cross the placenta, and concentrations reached in the umbilical vein approach those in the maternal plasma. Hydrochlorothiazide, like other diuretics, can cause placental hypoperfusion. It accumulates in the amniotic fluid, with reported concentrations up to 19 times higher than in umbilical vein plasma. Use of thiazides during pregnancy is associated with a risk of fetal or neonatal jaundice or thrombocytopenia. Since they do not prevent or alter the course of EPH (Edema, Proteinuria, Hypertension) gestosis (pre eclampsia), these drugs should not be used to treat hypertension in pregnant women. The use of hydrochlorothiazide for other indications (e.g. heart disease) in pregnancy should be avoided.

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

8.6 Renal Impairment

Safety and effectiveness of Tekturna HCT in patients with severe renal impairment (CrCl \leq 30 mL/min) have not been established. No dose adjustment is required in patients with mild (CrCl 60-90 mL/min) or moderate (CrCl 30-60) renal impairment.

8.7 Hepatic Impairment

Aliskiren

No dose adjustment is necessary for patients with mild-to-severe liver disease.

Hydrochlorothiazide

Minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.

14. Under **CLINICAL PHARMACOLOGY/Pharmacodynamics**, the following text was added:

Drug Interactions

Hydrochlorothiazide

Alcohol, barbiturates, or narcotics: Potentiation of orthostatic hypotension may occur.

Skeletal muscle relaxants: Possible increased responsiveness to muscle relaxants such as curare derivatives.

Digitalis glycosides: Thiazide-induced hypokalemia or hypomagnesemia may predispose the patient to digoxin toxicity.

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

Absorption and Distribution

Tekturna HCT

Following oral administration of Tekturna HCT combination tablets, the median peak plasma concentration time are within 1 hour for aliskiren and 2.5 hours for hydrochlorothiazide. When taken with food, mean AUC and C_{max} of aliskiren are decreased by 60% and 82%, respectively; mean AUC and C_{max} of hydrochlorothiazide increased by 13% and 10%, respectively. As a result, patients should establish a routine pattern for taking Tekturna HCT with regard to meals ~~and should be advised that high-fat meals decrease absorption of aliskiren substantially.~~

Hydrochlorothiazide

~~Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.~~

Aliskiren

Aliskiren is poorly absorbed (bioavailability about 2.5%). Following oral administration, peak plasma concentrations of aliskiren are reached within 1 to 3 hours. When taken with a high fat meal, mean AUC and C_{max} of aliskiren are decreased by 71% and 85% respectively. In the clinical trials of aliskiren, it was administered without requiring a fixed relation of administration to meals.

Hydrochlorothiazide

The estimated absolute bioavailability of hydrochlorothiazide after oral administration is about 70%. Peak plasma hydrochlorothiazide concentrations (C_{max}) are reached within 2 to 5 hours after oral administration. There is no clinically significant effect of food on the bioavailability of hydrochlorothiazide.

Hydrochlorothiazide binds to albumin (40 to 70%) and distributes into erythrocytes. Following oral administration, plasma hydrochlorothiazide concentrations decline bi-exponentially, with a mean distribution half-life of about 2 hours and an elimination half-life of about 10 hours.

Metabolism and Elimination

Aliskiren

The effective half-life for aliskiren is 24 hours. Steady state blood levels are reached in about 7 – 8 days. About one-fourth of the absorbed dose appears in the urine as parent drug. How much of the absorbed dose is metabolized is unknown. Based on the *in vitro* studies, the major enzyme responsible for aliskiren metabolism appears to be CYP 3A4. Aliskiren does not inhibit the CYP450 isoenzymes (CYP 1A2, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A) or induce CYP 3A4.

Transporters: Pgp (MDR1/Mdr1a/1b) was found to be the major efflux system involved in absorption and disposition of aliskiren in preclinical studies. The potential for drug interactions at the Pgp site will likely depend on the degree of inhibition of this transporter.

Hydrochlorothiazide

~~Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated as unchanged drug within 24 hours. The elimination half life is between 5.8 and 18.9 hours.~~

About 70% of an orally administered dose of hydrochlorothiazide is eliminated in the urine as unchanged drug.

Drug Interactions

Hydrochlorothiazide

Drugs that alter gastrointestinal motility: The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate. Conversely, prokinetic drugs may decrease the bioavailability of thiazide diuretics.

Cholestyramine: In a dedicated drug interaction study, administration of cholestyramine 2 hours before hydrochlorothiazide resulted in a 70% reduction in exposure to hydrochlorothiazide. Further, administration of hydrochlorothiazide 2 hours before cholestyramine, resulted in 35% reduction in exposure to hydrochlorothiazide.

Antineoplastic agents (e.g. cyclophosphamide, methotrexate): Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects.

Special Populations

Pediatric Patients

The pharmacokinetics of aliskiren have not been investigated in patients <18 years of age.

Geriatric Patients

Aliskiren

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 [See Dosage and Administration (2)].~~

Hydrochlorothiazide

A limited amount of data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.

Race

Too few non-Caucasians have been studied with Tekturna HCT to assess pharmacokinetic differences among races. The pharmacokinetic differences among Blacks, Caucasians, and Japanese are minimal with aliskiren therapy.

Renal Impairment

Aliskiren

The pharmacokinetics of aliskiren were evaluated in patients with varying degrees of renal impairment. Rate and extent of exposure (AUC and C_{max}) of aliskiren in subjects with renal impairment did not show a consistent correlation with the severity of renal impairment [*See Special Populations (8.6)*]. ~~Adjustment of the starting dose is not required in patients with mild or moderate renal impairment, but Tekturna HCT is not recommended in patients with severe renal impairment [*See Dosage and Administration (2) and Warnings and Precautions (5.4)*].~~

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 (C_{max} 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.

Hydrochlorothiazide

In a study in individuals with impaired renal function, the mean elimination half-life of hydrochlorothiazide was doubled in individuals with mild/moderate renal impairment (30 < CL_{cr} < 90 mL/min) and tripled in severe renal impairment (≤ 30 mL/min), compared to individuals with normal renal function (CL_{cr} > 90 mL/min) [*see Special Populations (8.6)*].

Hepatic Impairment

The pharmacokinetics of aliskiren were not significantly affected in patients with mild-to-severe liver disease [*see Special Populations (8.6)*]. ~~Consequently, adjustment of the starting dose is not required in these patients [*See Dosage and Administration (2)*].~~

16. Under **NON CLINICAL TOXICOLOGY/Carcinogenesis, Mutagenesis, Impairment of Fertility/Hydrochlorothiazide**, the words “was not teratogenic and” were added to the third paragraph

17. The revision date and version number were updated.

There are no other changes from the last approved package insert.

The following change was made to the Patient Information sheet:

- Under **Tell your doctor about all the medicines you take**, the ninth bullet was deleted:
 - Potassium supplements

2. The revision date and version number were updated.

There are no other changes from the last approved package insert.

We have completed our review of this supplemental application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending “Changes Being Effectuated” (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
02/14/2012