



NDA 020818/S-051

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals
Attention: Nancy Price
Executive Director DRA
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Price:

Please refer to your Supplemental New Drug Application (sNDA) dated and received July 7, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) Diovan HCT (valsartan/hydrochlorothiazide) 80/12.5 mg, 160/12.5 mg, 160/25 mg, 320/12.5 mg, and 320/25 mg Tablets.

This "Prior Approval" supplemental new drug application provides for labeling revised as follows (additions are shown as underlined text and deletions are shown as ~~striketrough text~~):

In HIGHLIGHTS:

1. Under **RECENT MAJOR CHANGES**, the following text was deleted:

~~-----RECENT MAJOR CHANGES-----~~

~~Indications and Usage: Benefits of lowering blood pressure (1) 12/2011~~

~~Warnings and Precautions: Acute Angle Closure Glaucoma (5.9) 2/2011~~

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

~~-----DOSAGE AND ADMINISTRATION-----~~

~~General considerations:~~

- ~~• Maximum effects within 2 to 4 weeks after dose change (2.1) Dose once daily. Titrate as needed to a maximum dose of 320/25mg (2)~~
- May be used as add-on/switch therapy for patients not adequately controlled on any of the components (valsartan or HCTZ). Renal impairment: Not recommended for patients with severe renal impairment (creatinine clearance \leq 30 mL/min) (2.1, 5.8)
- ~~• Diovan HCT may be administered with or without food.~~

~~Hypertension~~

- ~~• Add-on therapy OR Initial therapy: Initiate with 160/12.5 mg. Titrate upwards as needed to a maximum dose of 320/25 mg. One tablet daily (2.2, 2.4)~~
- ~~• Replacement therapy: m~~ May be substituted for titrated components (2.3)

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

-----**WARNINGS AND PRECAUTIONS**-----

- ~~Avoid fetal or neonatal exposure (5.1)~~
- ~~Symptomatic hypotension: with volume and/or salt depletion. Correct volume-depletion prior to initiation administration. Not recommended as initial therapy in volume-depleted patients (2.4, (5.2)~~
- ~~Use with caution in patients with impaired hepatic (5.3) or renal (5.8) Function~~
- ~~Observe for signs of fluid or electrolyte imbalance (5.7)~~
- ~~Monitor renal function in susceptible patients (5.3)~~
- ~~Thiazide diuretics may cause an exacerbation or activation of systemic lupus erythematosus (5.5)~~
- ~~Hydrochlorothiazide has been associated with Acute angle-closure glaucoma (5.9)~~

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

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

Hydrochlorothiazide (7):

- ~~Alcohol, barbiturates, narcotics: Potentiation of orthostatic hypotension~~
- ~~Antidiabetic drugs: Dosage adjustment of antidiabetic may be required~~
- ~~Cholestyramine and colestipol: Reduced absorption of thiazides~~
- ~~Corticosteroids, Adrenocorticotrophic Hormone (ACTH): Hypokalemia, electrolyte depletion~~
- ~~Lithium: Reduced renal clearance and high risk of lithium toxicity when used with diuretics. Should not be given with diuretics. Monitor serum lithium concentrations during concurrent use.~~
- ~~Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): May increase risk of renal impairment. Can reduce diuretic, natriuretic and antihypertensive effects of diuretics. Observe patient closely.~~

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

Add-On Therapy

Diovan HCT may be used in patients whose blood pressure is not adequately controlled on monotherapy.

Replacement Therapy

Diovan HCT may be substituted for the titrated components.

Initial Therapy

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

2.1 General Considerations

The side effects of valsartan are generally rare and appear independent of dose. Those of hydrochlorothiazide are a mixture of dose-dependent (primarily hypokalemia) and dose-independent phenomena (e.g., pancreatitis), the former much more common than the latter [see *Adverse Reactions* (6)].

~~Dose once daily. The usual starting dose is Diovan HCT 160/12.5 mg once daily. The dosage can be increased after 1 to 2 weeks of therapy to a maximum of one 320/25 tablet once daily as needed to control blood pressure [see Clinical Studies (14.2)]. Maximum antihypertensive effects are attained within 2 to 4 weeks after a change in dose.~~

~~Diovan HCT may be administered with or without food.~~

~~Diovan HCT may be administered with other antihypertensive agents.~~

~~Elderly patients: No initial dosage adjustment is required for elderly patients.~~

~~Renal impairment: The usual regimens of therapy with Diovan 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 Diovan HCT is not recommended.~~

~~Hepatic impairment: Care should be exercised with dosing of Diovan HCT in patients with hepatic impairment. Start with a low dose and titrate slowly in patients with hepatic impairment [see Warnings and Precautions (5.3)].~~

2.4 Initial Therapy

~~The usual starting dose is Diovan HCT 160/12.5 mg once daily. The dosage can be increased after 1 to 2 weeks of therapy to a maximum of one 320/25 mg tablet once daily as needed to control blood pressure [see Clinical Studies (14.2)]. Diovan HCT is not recommended as initial therapy in patients with intravascular volume depletion [see Warnings and Precautions (5.2)].~~

2.5 Use with Other Antihypertensive Drugs

~~Diovan HCT may be administered with other antihypertensive agents.~~

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

5.3 Impaired Hepatic Function

~~**Hydrochlorothiazide:** Thiazide diuretics should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.~~

~~**Valsartan:** As the majority of valsartan is eliminated in the bile, patients with mild to moderate hepatic impairment, including patients with biliary obstructive disorders, showed lower valsartan clearance (higher AUCs). Care should be exercised in administering Diovan (valsartan) to these patients.~~

5.3 Impaired Renal Function Heading

~~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 Diovan 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 Diovan HCT.

5.7 Serum Electrolytes-Abnormalities

Valsartan – Hydrochlorothiazide: In the controlled trials of various doses of the combination of valsartan and hydrochlorothiazide Diovan HCT the incidence of hypertensive patients who developed hypokalemia (serum potassium <3.5 mEq/L) was 3.0%; the incidence of hyperkalemia (serum potassium >5.7 mEq/L) was 0.4%. In controlled clinical trials of Diovan HCT (valsartan and hydrochlorothiazide, USP), the average change in serum potassium was near zero in subjects who received Diovan HCT 160/12.5 mg, 320/12.5 mg or 320/25 mg, but the average subject who received Diovan HCT 80/12.5 mg, 80/25 mg or 160/25 mg experienced a mild reduction 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.

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

In clinical trials, the opposite effects of valsartan (80, 160 or 320 mg) and hydrochlorothiazide (12.5 mg) on serum potassium approximately balanced each other in many patients. In other patients, one or the other effect may be dominant. Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

5.8 Impaired Renal Function

Valsartan: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with Diovan®.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. In a 4 day trial of valsartan in 12 patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long term use of valsartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

5.9 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 Diovan HCT.

8. Under **ADVERSE REACTIONS/Clinical Trials Experience/Hydrochlorothiazide**, the words “not listed above” were added to the first sentence.
9. Under **ADVERSE REACTIONS/Clinical Trials Experience**, a new section was added:

Clinical Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Diovan HCT.

Creatinine/Blood Urea Nitrogen (BUN): Minor elevations in creatinine and BUN occurred in 2% and 15% respectively, of patients taking Diovan HCT and 0.4% and 6% respectively, given placebo in controlled clinical trials.

Hemoglobin and Hematocrit: Greater than 20% decreases in hemoglobin and hematocrit were observed in less than 0.1% of Diovan HCT patients, compared with 0% in placebo-treated patients.

Liver Function Tests: Occasional elevations (greater than 150%) of liver chemistries occurred in Diovan HCT-treated patients.

Neutropenia: Neutropenia was observed in 0.1% of patients treated with Diovan HCT and 0.4% of patients treated with placebo.

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

The following additional adverse reactions have been reported in valsartan or valsartan/hydrochlorothiazide postmarketing experience. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity: There are rare reports of angioedema;

Digestive: Elevated liver enzymes and very rare reports of hepatitis;

Renal: Impaired renal function;

Clinical Laboratory Tests: Hyperkalemia;

Dermatologic: Alopecia;

Vascular: Vasculitis;

Nervous System: Syncope.

Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

~~Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.~~

Hydrochlorothiazide:

The following additional adverse reactions have been reported in post-marketing experience with 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, hypochloremic 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 text added/deleted:

7 DRUG INTERACTIONS

Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including valsartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving valsartan and NSAID therapy.

The antihypertensive effect of angiotensin II receptor antagonists, including valsartan may be attenuated by NSAIDs including selective COX-2 inhibitors.

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 relaxant.~~

~~*Lithium* - Should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with Diovan HCT. Monitoring of serum lithium concentrations is recommended during concurrent use.~~

~~*Nonsteroidal Anti-inflammatory Drug (NSAIDs and COX-2 selective inhibitors)*- - 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 Diovan 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.~~

~~*Carbamazepine* – May lead to symptomatic hyponatremia.~~

~~*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)]~~

~~*Cyclosporine:* Concomitant treatment with cyclosporine may increase the risk of hyperuricemia and gout-type complications.~~

~~**7.3 Clinical Laboratory Test Findings**~~

~~In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Diovan HCT.~~

~~***Creatinine/Blood Urea Nitrogen (BUN):*** Minor elevations in creatinine and BUN occurred in 2% and 15% respectively, of patients taking Diovan HCT and 0.4% and 6% respectively, given placebo in controlled clinical trials.~~

~~**Hemoglobin and Hematocrit:** Greater than 20% decreases in hemoglobin and hematocrit were observed in less than 0.1% of Diovan HCT patients, compared with 0.0% in placebo treated patients.~~

~~**Liver Function Tests:** Occasional elevations (greater than 150%) of liver chemistries occurred in Diovan HCT treated patients.~~

~~**Neutropenia:** Neutropenia was observed in 0.1% of patients treated with Diovan HCT and 0.4% of patients treated with placebo.~~

~~**Serum Electrolytes:** [see Warnings and Precautions (5.7)].~~

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

8.1 Pregnancy

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.

8.6 Renal Impairment

Safety and effectiveness of Diovan 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

Valsartan

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

Hydrochlorothiazide

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

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

12.2 Pharmacodynamics

Valsartan: Valsartan inhibits the pressor effect of angiotensin II infusions. An oral dose of 80 mg inhibits the pressor effect by about 80% at peak with approximately 30% inhibition persisting for 24 hours. No information on the effect of larger doses is available. Removal of the negative feedback of angiotensin II causes a 2- to 3-fold rise in plasma renin and consequent rise in angiotensin II plasma concentration in hypertensive patients. Minimal decreases in plasma aldosterone were observed after administration of valsartan; very little effect on serum potassium was observed.

~~In multiple dose studies in hypertensive patients with stable renal insufficiency and patients with renovascular hypertension, valsartan had no clinically significant effects on glomerular filtration rate, filtration fraction, creatinine clearance, or renal plasma flow.~~

~~In multiple dose studies in hypertensive patients, valsartan had no notable effects on total cholesterol, fasting triglycerides, fasting serum glucose, or uric acid.~~

Hydrochlorothiazide: After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

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.

12.3 Pharmacokinetics

Valsartan: Valsartan peak plasma concentration is reached 2 to 4 hours after dosing. Valsartan shows bi-exponential decay kinetics following intravenous administration, with an average elimination half-life of about 6 hours. Absolute bioavailability for the capsule formulation is about 25% (range 10%-35%). Food decreases the exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%. AUC and C_{max} values of valsartan increase approximately linearly with increasing dose over the clinical dosing range. Valsartan does not accumulate appreciably in plasma following repeated administration.

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.

~~Thiazide diuretics are eliminated by the kidney, with a terminal half life of 5-15 hours.~~

~~**Geriatric:** Exposure (measured by AUC) to valsartan is higher by 70% and the half life is longer by 35% in the elderly than in the young. No dosage adjustment is necessary [*see Dosage and Administration (2.1)*].~~

~~**Gender:** Pharmacokinetics of valsartan does not differ significantly between males and females.~~

~~**Race:** Pharmacokinetic differences due to race have not been studied.~~

~~**Renal Insufficiency:** There is no apparent correlation between renal function (measured by creatinine clearance) and exposure (measured by AUC) to valsartan in patients with different degrees of renal impairment. Consequently, dose adjustment is not required in patients with mild to moderate renal dysfunction. No studies have been performed in patients with severe impairment of renal function (creatinine clearance <10 mL/min). Valsartan is not removed from the plasma by hemodialysis. In the case of severe renal disease, exercise care with dosing of valsartan [*see Dosage and Administration (2.1)*].~~

~~In a study of patients with impaired renal function (mean creatinine clearance of 19 mL/min), the half life of hydrochlorothiazide elimination was lengthened to 21 hours.~~

~~**Hepatic Insufficiency:** On average, patients with mild to moderate chronic liver disease have twice the exposure (measured by AUC values) to valsartan of healthy volunteers (matched by age, sex, and weight). In general, no dosage adjustment is needed in patients with mild to moderate liver disease. Care should be exercised in patients with liver disease [*see Dosage and Administration (2.1)*].~~

Diovan HCT: Diovan HCT may be administered with or without food

Distribution

Valsartan: The steady state volume of distribution of valsartan after intravenous administration is small (17 L), indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (95%), mainly serum albumin.

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

Metabolism

Valsartan: The primary metabolite, accounting for about 9% of dose, is valeryl 4-hydroxy valsartan. In vitro metabolism studies involving recombinant CYP 450 enzymes indicated that the CYP 2C9 isoenzyme is responsible for the formation of valeryl-4-hydroxy valsartan. Valsartan does not inhibit CYP 450 isozymes at clinically relevant concentrations. CYP 450 mediated drug interaction between valsartan and co-administered drugs are unlikely because of the low extent of metabolism.

Hydrochlorothiazide: Is not metabolized.

Excretion

Valsartan: Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). The recovery is mainly as unchanged drug, with only about 20% of dose recovered as metabolites. Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance).

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.

Special Populations

Geriatric: Exposure (measured by AUC) to valsartan is higher by 70% and the half-life is longer by 35% in the elderly than in the young. 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.

Gender: Pharmacokinetics of valsartan does not differ significantly between males and females.

Race: Pharmacokinetic differences due to race have not been studied.

Renal Insufficiency: There is no apparent correlation between renal function (measured by creatinine clearance) and exposure (measured by AUC) to valsartan in patients with different degrees of renal impairment. Valsartan has not been studied in patients with severe impairment of renal function (creatinine clearance <10 mL/min). Valsartan is not removed from the plasma by hemodialysis.

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 Use in Specific Populations (8.6)].

Hepatic Insufficiency: On average, patients with mild-to-moderate chronic liver disease have twice the exposure (measured by AUC values) to valsartan of healthy volunteers (matched by age, sex, and weight). [see Use in Specific Populations (8.7)].

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.

In the FDA-Approved Patient Labeling:

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

Tell your doctor about all your medical conditions including if you:

- **are pregnant or plan to become pregnant.** See “What is the most important information I should know about DIOVAN HCT?”
- **are breast-feeding.** DIOVAN HCT passes into breast milk. You should choose either to take DIOVAN HCT or breast-feed, but not both.
- **have liver problems**
- **have kidney problems**
- **have or had gallstones**
- **have Lupus**
- **have low levels of potassium** (with or without symptoms such as muscle weakness, muscle spasms, abnormal heart rhythm) or **magnesium in your blood**

(b) (4)

- **have high levels of calcium in your blood** (with or without symptoms such as nausea, vomiting, constipation, stomach pain, frequent urination, thirst, muscle weakness and twitching).
- **have high levels of uric acid in the blood.**

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. Some of your other medicines and DIOVAN HCT could affect each other, causing serious side effects. Especially, tell your doctor if you take:

- other medicines for high blood pressure or a heart problem
- water pills (diuretics)
- potassium supplements
- a salt substitute containing potassium
- antidiabetic medicines including insulin
- narcotic pain medicines
- sleeping pills

- lithium, a medicine used in some types of depression (Eskalith[®], Lithobid[®], Lithium Carbonate, Lithium Citrate)
- aspirin or other medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), like ibuprofen or naproxen
- digoxin or other digitalis glycosides (a heart medicine)
- muscle relaxants (medicines used during operations)
- certain cancer medicines, like cyclophosphamide or methotrexate

Ask your doctor if you are not sure if you are taking one of these medicines. Know the medicines you take. Keep a list of your medicines with you to show to your doctor and pharmacist when a new medicine is prescribed. Talk to your doctor or pharmacist before you start taking any new medicine. Your doctor or pharmacist will know what medicines are safe to take together.

2. Under What are the possible side effects of DIOVAN HCT?, the following text was deleted:

DIOVAN HCT may cause serious side effects including:

- **Harm to an unborn baby causing injury and even death.** See “What is the most important information I should know about DIOVAN HCT?”
- **Low blood pressure (hypotension).** Low blood pressure is most likely to happen if you:
 - take water pills
 - are on a low salt diet
 - get dialysis treatments
 - have heart problems
 - get sick with vomiting or diarrhea
 - drink alcohol

Lie down if you feel faint or dizzy. Call your doctor right away.

- ~~**Worsening liver problems.** Liver problems may get worse in people who already have liver problems and take DIOVAN HCT.~~
- **Allergic reactions.** People with and without allergy problems or asthma who take DIOVAN HCT may get allergic reactions.
- **Worsening of Lupus.** Hydrochlorothiazide, one of the medicines in DIOVAN HCT may cause Lupus to become active or worse.
- **Fluid and electrolyte (salt) problems.** Tell your doctor about any of the following signs and symptoms of fluid and electrolyte problems:

- dry mouth
- thirst
- lack of energy (lethargic)
- weakness
- drowsiness
- restlessness
- confusion
- seizures
- muscle pain or cramps
- muscle fatigue
- very low urine output
- fast heartbeat
- nausea and vomiting

- **Kidney problems.** Kidney problems may become worse in people that already have kidney disease. Some people will have changes on blood tests for kidney function and may need a lower dose of DIOVAN HCT. Call your doctor if you get swelling in your feet, ankles, or hands, or unexplained weight gain. If you have heart failure, your doctor should check your kidney function before prescribing DIOVAN HCT.
- **Skin rash.** Call your doctor right away if you have an unusual skin rash.
- **Eye Problems.** One of the medicines in DIOVAN HCT can cause eye problems that may lead to vision loss. Symptoms of eye problems can happen within hours to weeks of starting DIOVAN HCT.

Tell your doctor right away if you have:

- decrease in vision
- eye pain

Other side effects were generally mild and brief. They generally have not caused patients to stop taking DIOVAN HCT.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of DIOVAN HCT. For a complete list, 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.

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(1)(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
02/16/2012