



NDA 022314/S-009

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Nancy Price
Global Program Regulatory Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

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) for Exforge HCT (amlodipine/valsartan/hydrochlorothiazide) 5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg, and 10/320/25 mg Tablets (NDA 022314).

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

1. In **HIGHLIGHTS/WARNINGS AND PRECAUTIONS**, 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 (5.11) 2/2011~~

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

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

- Dose once-daily. Titrate up to a maximum dose of 10/320/25 mg
- Exforge HCT may be used as add-on/switch therapy for patients not adequately controlled on any two of the following antihypertensive classes: calcium channel blockers, angiotensin receptor blockers, and diuretics.
- Exforge HCT may be substituted for its individually titrated components ~~for patients on amlodipine, valsartan and hydrochlorothiazide (2)~~.
- ~~The full blood pressure lowering effect was achieved 2 weeks after being on the maximal dose of Exforge HCT (2)~~.

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

~~-----WARNINGS AND PRECAUTIONS-----~~

- ~~Avoid fetal or neonatal exposure (5.1)~~
- ~~Symptomatic Hypotension with volume or salt depletion. Correct volume-depletion prior to initiation administration (5.2)~~
- Increased angina and/or myocardial infarction (5.3)

- Monitor renal function in susceptible patients. (5.4)
- ~~Avoid in patients with severely impaired hepatic (2.1, 5.4) or renal function (creatinine clearance \leq 30 mL/min) (2.1, 5.5)~~
- Observe for signs of fluid or electrolyte imbalance (5.10)
- ~~Thiazide diuretics may cause an exacerbation or activation of systemic lupus erythematosus (5.87)~~
- ~~Hydrochlorothiazide has been associated with an acute angle-closure glaucoma (5.110)~~

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

~~-----DRUG INTERACTIONS-----~~
Hydrochlorothiazide (7):

- If simvastatin is co-administered with amlodipine, do not exceed doses greater than 20 mg daily of simvastatin (7)
- ~~Alcohol, barbiturates, narcotics: Potentiation of orthostatic hypotension~~
- Antidiabetic drugs: Dosage adjustment of antidiabetic may be required (7)
- Cholestyramine and colestipol: Reduced absorption of thiazides (7)
- ~~Corticosteroids, ACTH: Hypokalemia, electrolyte depletion~~
- Lithium: Reduced renal clearance and high Diuretics increase risk of lithium toxicity when used with diuretics. Should not be given with diuretics. Monitor serum lithium concentrations during concurrent use (7)
- NSAIDs: May increase risk of renal impairment. Can reduce diuretic, natriuretic and antihypertensive effects of diuretics.

5. In **HIGHLIGHTS/USE IN SPECIFIC POPULATIONS**, the following text was added/deleted:

~~-----USE IN SPECIFIC POPULATIONS-----~~

~~Pregnancy: Avoid use in pregnancy (5.1)~~

~~Nursing Mothers: Avoid use while nursing – discontinue either nursing or drug (8.3)~~

~~Geriatric Patients: No overall differences in the efficacy or safety of Exforge HCT was observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out. (8.5)~~

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

2.1 General Considerations

Dose once-daily. The dosage may be increased after two weeks of therapy. The full blood pressure lowering effect was achieved 2 weeks after being on the maximal dose of Exforge HCT. The maximum recommended dose of Exforge HCT is 10/320/25 mg.

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

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

Renal impairment: ~~The usual regimens of therapy with Exforge HCT may be followed if the patient's creatinine clearance is $>$ 30 mL/min. In patients with~~

~~more severe renal impairment, loop diuretics are preferred to thiazides, so avoid use of Exforge HCT [see *Impaired Renal Function* (5.5)].~~

~~**Hepatic impairment:** Avoid Exforge HCT in patients with severe hepatic impairment. In patients with lesser degrees of hepatic impairment, monitor for worsening of hepatic or renal function and adverse reactions [see *Impaired Hepatic Function* (5.4)].~~

7. Under **DOSAGE AND ADMINISTRATION**, a new section was added:

2.4 Use with Other Antihypertensive Drugs

Exforge HCT may be administered with other antihypertensive agents.

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

5.4 Impaired Hepatic Function

~~Amlodipine is extensively metabolized by the liver and the plasma elimination half life ($t_{1/2}$) is 56 hours in patients with impaired hepatic function.~~

~~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).~~

~~In patients with impaired hepatic function or progressive liver disease, minor alterations of fluid and electrolyte balance, such as those resulting from diuretic use, may precipitate hepatic coma.~~

~~Therefore, avoid the use of Exforge HCT in patients with severe hepatic impairment. When administering Exforge HCT to patients with mild to moderate hepatic impairment, including patients with biliary obstructive disorders, monitor for worsening of hepatic or renal function, including fluid status and electrolytes, and adverse reactions.~~

5.5 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 Exforge 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 Exforge HCT.

~~As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, 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 valsartan.~~

~~In studies of ACE inhibitors in hypertensive 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 hypertensive 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.~~

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

~~Avoid use of Exforge HCT in severe renal disease (creatinine clearance \leq 30 mL/min). The usual regimens of therapy with Exforge HCT may be followed if the patient's creatinine clearance is $>$ 30 mL/min.~~

~~There is no experience in the use of Exforge HCT in patients with a recent kidney transplant.~~

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

5.109 Electrolytes and Metabolic Imbalances

Amlodipine -Valsartan - Hydrochlorothiazide

In the controlled trial of Exforge HCT in moderate to severe hypertensive patients, the incidence of hypokalemia (serum potassium $<$ 3.5 mEq/L) at any time post-baseline with the maximum dose of Exforge HCT (10/320/25 mg) was 10% compared to 25% with HCTZ/amlodipine (25/10 mg), 7% with valsartan/HCTZ (320/25 mg), and 3% with amlodipine/valsartan (10/320 mg). One patient (0.2%) discontinued therapy due to an adverse event of hypokalemia in each of the Exforge HCT and HCTZ/amlodipine groups. The incidence of hyperkalemia (serum potassium $>$ 5.7 mEq/L) was 0.4% with Exforge HCT compared to 0.2-0.7% with the dual therapies.

Monitor serum electrolytes periodically based on Exforge HCT use and other factors such as renal function, other medications, or history of prior electrolyte imbalances.

Hydrochlorothiazide

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), Exforge HCT should be discontinued. Correction of hypokalemia and any coexisting hypomagnesemia is recommended prior to the initiation of thiazides.

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 Exforge HCT.

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients, dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident, consider withholding or discontinuing Exforge HCT therapy or substituting other antihypertensive therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in

~~hypomagnesemia.~~

~~Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Exforge HCT should be discontinued or non-thiazide antihypertensive therapy substituted before carrying out tests for parathyroid function.~~

~~Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.~~

10. Under **ADVERSE REACTIONS/Clinical Trials Experience**, the following text was added:

Clinical Laboratory Test Findings

Clinical laboratory test findings for Exforge HCT were obtained in a controlled trial of Exforge HCT administered at the maximal dose of 10/320/25 mg compared to maximal doses of dual therapies, i.e. valsartan/HCTZ 320/25 mg, amlodipine/valsartan 10/320 mg, and HCTZ/amlodipine 25/10 mg. Findings for the components of Exforge HCT were obtained from other trials.

Creatinine: In hypertensive patients, greater than 50% increases in creatinine occurred in 2.1% of Exforge HCT patients compared to 2.4% of valsartan/HCTZ patients, 0.7% of amlodipine/valsartan patients, and 1.8% of HCTZ/amlodipine patients.

In heart failure patients, greater than 50% increases in creatinine were observed in 3.9% of valsartan-treated patients compared to 0.9% of placebo-treated patients. In post-myocardial infarction patients, doubling of serum creatinine was observed in 4.2% of valsartan-treated patients and 3.4% of captopril-treated patients.

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

Blood Urea Nitrogen (BUN): In hypertensive patients, greater than 50% increases in BUN were observed in 30% of Exforge HCT-treated patients compared to 29% of valsartan/HCTZ patients, 15.8% of amlodipine/valsartan patients, and 18.5% of HCTZ/amlodipine patients. The majority of BUN values remained within normal limits.

In heart failure patients, greater than 50% increases in BUN were observed in 17% of valsartan-treated patients compared to 6% of placebo-treated patients.

Serum Electrolytes (Potassium): In hypertensive patients, greater than 20% decreases in serum potassium were observed in 6.5% of Exforge HCT-treated patients compared to 3.3% of valsartan/HCTZ patients, 0.4% of amlodipine/valsartan patients, and 19.3% of HCTZ/amlodipine patients. Greater than 20% increases in potassium were observed in 3.5% of Exforge HCT-treated patients compared to 2.4% of valsartan/HCTZ patients, 6.2% of amlodipine/valsartan patients, and 2.2% of HCTZ/amlodipine patients.

In heart failure patients, greater than 20% increases in serum potassium were observed in 10% of valsartan-treated patients compared to 5.1% of placebo-treated patients [see *Warnings and Precautions, Electrolytes and Metabolic Imbalances* (5.10)].

Neutropenia: Neutropenia (<1500/L) was observed in 1.9% of patients treated with valsartan and 0.8% of patients treated with placebo.

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

6.2 Post-Marketing Experience

The following additional adverse reactions have been reported in post marketing 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.

Amlodipine

With amlodipine, gynecomastia has been reported infrequently and a causal relationship is uncertain. Jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalization, have been reported in association with use of amlodipine.

Valsartan

The following additional adverse reactions have been reported in post-marketing experience with valsartan or valsartan/hydrochlorothiazide:

Blood and Lymphatic: There are very rare reports of thrombocytopenia.

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.

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

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 increase the 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 Exforge HCT. Monitoring of serum lithium concentrations is recommended during concurrent use.~~

~~*Non-steroidal anti-inflammatory drugs (NSAIDs and COX-2 selective inhibitors):* In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium sparing and thiazide diuretics.~~

When Exforge HCT and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of 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.

7.1 Clinical Laboratory Test Findings

Clinical laboratory test findings for Exforge HCT were obtained in a controlled trial of Exforge HCT administered at the maximal dose of 10/320/25 mg compared to maximal doses of dual therapies, i.e. valsartan/HCTZ 320/25 mg, amlodipine/valsartan 10/320 mg, and HCTZ/amlodipine 25/10 mg. Findings for the components of Exforge HCT were obtained from other trials.

Creatinine: In hypertensive patients, greater than 50% increases in creatinine occurred in 2.1% of Exforge HCT patients compared to 2.4% of valsartan/HCTZ patients, 0.7% of amlodipine/valsartan patients, and 1.8% of HCTZ/amlodipine patients.

In heart failure patients, greater than 50% increases in creatinine were observed in 3.9% of valsartan treated patients compared to 0.9% of placebo treated patients. In post myocardial infarction patients, doubling of serum creatinine was observed in 4.2% of valsartan treated patients and 3.4% of captopril treated patients.

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

Blood Urea Nitrogen (BUN): In hypertensive patients, greater than 50% increases in BUN were observed in 30% of Exforge HCT treated patients compared to 29% of valsartan/HCTZ patients, 15.8% of amlodipine/valsartan patients, and 18.5% of HCTZ/amlodipine patients. The majority of BUN values remained within normal limits.

In heart failure patients, greater than 50% increases in BUN were observed in 17% of valsartan treated patients compared to 6% of placebo treated patients.

Serum Electrolytes (Potassium): In hypertensive patients, greater than 20% decreases in serum potassium were observed in 6.5% of Exforge HCT treated patients compared to 3.3% of valsartan/HCTZ patients, 0.4% of

amlodipine/valsartan patients, and 19.3% of HCTZ/amlodipine patients. Greater than 20% increases in potassium were observed in 3.5% of Exforge HCT treated patients compared to 2.4% of valsartan/HCTZ patients, 6.2% of amlodipine/valsartan patients, and 2.2% of HCTZ/amlodipine patients.

In heart failure patients, greater than 20% increases in serum potassium were observed in 10% of valsartan treated patients compared to 5.1% of placebo-treated patients [see Warnings and Precautions, Electrolytes and Metabolic Imbalances (5.10)].

Neutropenia: Neutropenia (<1500/L) was observed in 1.9% of patients treated with valsartan and 0.8% of patients treated with placebo.

7.3 Drug/Food Interactions

The bioavailability of amlodipine, valsartan, and HCTZ were not altered when Exforge HCT was administered with food.

13. Under **USE IN SPECIFIC POPULATIONS/Pregnancy**, 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 required 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 of 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.

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

8.6 Renal Impairment

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

8.7 Hepatic Impairment

Amlodipine

Amlodipine is extensively metabolized by the liver and the plasma elimination half-life (t_{1/2}) is 56 hours in patients with impaired hepatic function.

Valsartan

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

Hydrochlorothiazide

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

15. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics/Hydrochlorothiazide**, the section was changed from:

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

To:

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. Hydrochlorothiazide is eliminated from plasma with a half-life averaging 6 to 15 hours in the terminal elimination phase. Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

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

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.~~

Administration of valsartan to patients with essential hypertension results in a significant reduction of sitting, supine, and standing systolic blood pressure, usually with little or no orthostatic change.

Valsartan has indications other than hypertension which are described in its full prescribing information.

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.

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

Exforge HCT

Following oral administration of Exforge HCT in normal healthy adults, peak plasma concentrations of amlodipine, valsartan and HCTZ are reached in about 6 hours, 3 hours, and 2 hours, respectively. The rate and extent of absorption of amlodipine, valsartan and HCTZ from Exforge HCT are the same as when administered as individual dosage forms.

The bioavailability of amlodipine, valsartan, and HCTZ were not altered when Exforge HCT was administered with food. Exforge HCT may be administered with or without food.

Amlodipine

Peak plasma concentrations of amlodipine are reached 6-12 hours after administration of amlodipine alone. Absolute bioavailability has been estimated to be between 64% and 90%. The apparent volume of distribution of amlodipine is 21 L/kg. Approximately 93% of circulating amlodipine is bound to plasma proteins in hypertensive patients.

Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine.

Elimination of amlodipine from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours. Steady state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Valsartan

Following oral administration of valsartan alone peak plasma concentrations of valsartan are reached in 2 to 4 hours. Absolute bioavailability is about 25% (range 10%-35%).

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

Valsartan shows bi-exponential decay kinetics following intravenous administration with an average elimination half-life of about 6 hours. The recovery is mainly as unchanged drug, with only about 20% of dose recovered as metabolites. The primary metabolite, accounting for about 9% of dose, is valeryl 4-hydroxy valsartan. In vitro

metabolism studies involving recombinant CYP450 enzymes indicated that the CYP2C9 isoenzyme is responsible for the formation of valeryl-4-hydroxy valsartan. Valsartan does not inhibit CYP450 isozymes at clinically relevant concentrations. CYP450 mediated drug interaction between valsartan and co-administered drugs are unlikely because of the low extent of metabolism.

Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). 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. Hydrochlorothiazide crosses the placental but not the blood brain barrier and is excreted in breast milk.~~

Geriatric

~~**Studies with amlodipine:** Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40% - 60%; therefore a lower initial dose of amlodipine may be required.~~

~~**Studies with valsartan:** 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.~~

Gender

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

Renal Insufficiency

~~**Studies with amlodipine:** The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.~~

~~**Studies with valsartan:** 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.~~

~~**Studies with hydrochlorothiazide:** The half life of hydrochlorothiazide elimination was lengthened to 21 hours in a study of patients with impaired renal function (mean creatinine clearance of 19 mL/min).~~

Hepatic Insufficiency

Studies with amlodipine: Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40%-60%; therefore, a lower initial dose of amlodipine may be required.

Studies with valsartan: 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.

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

Special Populations

Geriatric: Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40%-60%. 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: The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. 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 < CLcr < 90 mL/min) and tripled in severe renal impairment (≤ 30 mL/min), compared to individuals with normal renal function (CLcr > 90 mL/min). [see Use in Special Populations (8.6)]

Hepatic Insufficiency: Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40%-60%. 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 Special 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.

18. The revision date and version number were updated.

The following changes were made to the Information for Patients section of the label:

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

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

- **are pregnant or plan to become pregnant.** See “What is the most important information I should know about EXFORGE HCT?”
- **are breast-feeding or plan to breast-feed.** EXFORGE HCT may pass into your milk. Do not breast-feed while you are taking EXFORGE HCT.
- are allergic to any of the ingredients in EXFORGE HCT. See the end of this leaflet for a list of the ingredients in EXFORGE HCT.
- have heart problems
- have liver problems
- have kidney problems
- are vomiting or having a lot of diarrhea
- 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 EXFORGE 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 or using a salt substitute containing potassium
- diabetes medicine including insulin
- narcotic pain medicines
- sleeping pills and anti-seizure medicines called barbiturates
- lithium, a medicine used to treat some types of depression
- aspirin or other medicines called non-steroidal anti-inflammatory drugs (NSAIDs), like ibuprofen or naproxen
- steroids
- cholesterol lowering medicine
- alcohol
- digoxin or other digitalis glycosides (a heart medicine)
- muscle relaxants (medicines used during operations)
- certain cancer medicines, like cyclophosphamide or methotrexate

Know the medicines you take. Keep a list of your medicines and show it to your doctor or pharmacist when you get a new medicine.

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, 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