

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EXFORGE HCT safely and effectively. See full prescribing information for EXFORGE HCT.

EXFORGE HCT® (amlodipine, valsartan, hydrochlorothiazide) tablets, for oral use

Initial U.S. Approval: 2009

WARNING: FETAL TOXICITY

See full prescribing information for complete boxed warning.

- When pregnancy is detected, discontinue Exforge HCT as soon as possible. (5.1)
- Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. (5.1)

INDICATIONS AND USAGE

Exforge HCT is a combination tablet of amlodipine, a dihydropyridine calcium channel blocker (DHP CCB), valsartan, an angiotensin II receptor blocker (ARB), and hydrochlorothiazide, a thiazide diuretic. Exforge HCT is indicated for the treatment of hypertension to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes, and myocardial infarctions. (1)

Limitation of Use

Exforge HCT is not indicated for initial treatment of hypertension.

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 (2)

DOSAGE FORMS AND STRENGTHS

Tablets: (amlodipine/valsartan/hydrochlorothiazide mg) 5/160/12.5, 10/160/12.5, 5/160/25, 10/160/25, 10/320/25 (3)

CONTRAINDICATIONS

- Anuria (4)
- Hypersensitivity to sulfonamide-derived drugs (4)
- Known hypersensitivity to any component (4)

- Do not coadminister aliskiren with Exforge HCT in patients with diabetes (4)

WARNINGS AND PRECAUTIONS

- Hypotension: Correct volume depletion prior to initiation (5.2)
- Increased angina and/or myocardial infarction (5.3)
- Monitor renal function and potassium in susceptible patients (5.4, 5.5)
- Exacerbation or activation of systemic lupus erythematosus (5.7)
- Observe for signs of fluid or electrolyte imbalance (5.9)
- Acute angle-closure glaucoma (5.10)

ADVERSE REACTIONS

Most common adverse events ($\geq 2\%$ incidence) are dizziness, peripheral edema, headache, dyspepsia, fatigue, muscle spasms, back pain, nausea, and nasopharyngitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- If simvastatin is coadministered with amlodipine, do not exceed doses greater than 20 mg daily of simvastatin (7)
- Antidiabetic drugs: Dosage adjustment of antidiabetic may be required (7)
- Cholestyramine and colestipol: Reduced absorption of thiazides (12.3)
- Lithium: Increased risk of lithium toxicity. Monitor serum lithium concentrations during concurrent use. (7)
- Non-Steroidal Anti-Inflammatory Drug (NSAID) use may lead to increased risk of renal impairment and loss of anti-hypertensive effect (7)
- Dual inhibition of the renin-angiotensin system: Increased risk of renal impairment, hypotension, and hyperkalemia (7)

USE IN SPECIFIC POPULATIONS

Lactation: Breastfeeding is not recommended (8.2)

Geriatric Patients: Not recommended for initial therapy (8.5)

Hepatic Impairment: Not recommended for initial therapy (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

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FULL PRESCRIBING INFORMATION

WARNING: FETAL TOXICITY

- **When pregnancy is detected, discontinue Exforge HCT as soon as possible. (5.1)**
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. (5.1)**

1 INDICATIONS AND USAGE

Exforge HCT (amlodipine, valsartan, hydrochlorothiazide) is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes, including amlodipine, hydrochlorothiazide, and the ARB class to which valsartan principally belongs. There are no controlled trials demonstrating risk reduction with Exforge HCT.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than 1 drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (e.g., patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

Limitation of Use

Exforge HCT is not indicated for the initial therapy of hypertension [*see Dosage and Administration (2)*].

2 DOSAGE AND ADMINISTRATION

2.1 General Considerations

Dose once-daily. The dosage may be increased after 2 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.

2.2 Add-on / Switch Therapy

Exforge HCT may be used for patients not adequately controlled on any 2 of the following antihypertensive classes: calcium channel blockers, angiotensin receptor blockers, and diuretics.

A patient who experiences dose-limiting adverse reactions to an individual component while on any dual combination of the components of Exforge HCT may be switched to Exforge HCT containing a lower dose of that component to achieve similar blood pressure reductions.

2.3 Replacement Therapy

Exforge HCT may be substituted for the individually titrated components.

2.4 Use with Other Antihypertensive Drugs

Exforge HCT may be administered with other antihypertensive agents.

3 DOSAGE FORMS AND STRENGTHS

- 5 mg amlodipine /160 mg valsartan /12.5 mg hydrochlorothiazide Tablets – White, non-scored, film-coated tablet, ovaloid, biconvex with beveled edge with debossing “NVR” on one side and “VCL” on the other side.
- 10 mg amlodipine /160 mg valsartan /12.5 mg hydrochlorothiazide Tablets – Pale yellow, non-scored, film-coated tablet, ovaloid, biconvex with beveled edge with debossing “NVR” on one side and “VDL” on the other side.
- 5 mg amlodipine /160 mg valsartan /25 mg hydrochlorothiazide Tablets – Yellow, non-scored, film-coated tablet, ovaloid, biconvex with beveled edge with debossing “NVR” on one side and “VEL” on the other side.
- 10 mg amlodipine /160 mg valsartan /25 mg hydrochlorothiazide Tablets – Brown-yellow, non-scored, film-coated tablet, ovaloid, biconvex with beveled edge with debossing “NVR” on one side and “VHL” on the other side.
- 10 mg amlodipine /320 mg valsartan /25 mg hydrochlorothiazide Tablets – Brown-yellow, non-scored, film-coated tablet, ovaloid, biconvex with beveled edge with debossing “NVR” on one side and “VFL” on the other side.

4 CONTRAINDICATIONS

Do not use in patients with anuria, hypersensitivity to other sulfonamide-derived drugs, or hypersensitivity to any component of this product.

Do not coadminister aliskiren with Exforge HCT in patients with diabetes [*see Drug Interactions (7)*].

5 WARNINGS AND PRECAUTIONS

5.1 Fetal Toxicity

Valsartan

Exforge HCT can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Exforge HCT as soon as possible [*see Use in Specific Populations (8.1)*].

Hydrochlorothiazide

Thiazides cross the placenta, and use of thiazides during pregnancy is associated with fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

5.2 Hypotension in Volume- or Salt-Depleted Patients

Excessive hypotension, including orthostatic hypotension, was seen in 1.7% of patients treated with the maximum dose of Exforge HCT (10/320/25 mg) compared to 1.8% of valsartan/HCTZ (320/25 mg) patients, 0.4% of amlodipine/valsartan (10/320 mg) patients, and 0.2% of HCTZ/amlodipine (25/10 mg) patients in a

controlled trial in patients with moderate to severe uncomplicated hypertension. In patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur in patients receiving angiotensin receptor blockers. Correct this condition prior to administration of Exforge HCT.

Exforge HCT has not been studied in patients with heart failure, recent myocardial infarction, or in patients undergoing surgery or dialysis. Patients with heart failure or post-myocardial infarction patients given valsartan commonly have some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed. In controlled trials in heart failure patients, the incidence of hypotension in valsartan-treated patients was 5.5% compared to 1.8% in placebo-treated patients. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), hypotension in post-myocardial infarction patients led to permanent discontinuation of therapy in 1.4% of valsartan-treated patients and 0.8% of captopril-treated patients.

Since the vasodilation induced by amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration. Do not initiate treatment with Exforge HCT in patients with aortic or mitral stenosis or obstructive hypertrophic cardiomyopathy.

If excessive hypotension occurs with Exforge HCT, place the patient in a supine position and, if necessary, give intravenous normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

5.3 Increased Angina and/or Myocardial Infarction

Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of amlodipine, particularly in patients with severe obstructive coronary artery disease.

5.4 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 [*see Drug Interactions (7)*].

5.5 Potassium Abnormalities

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% to 0.7% with the dual therapies.

Some patients with heart failure have developed increases in potassium on valsartan. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or valsartan may be required.

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.

5.6 Hypersensitivity Reaction

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

5.7 Systemic Lupus Erythematosus

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

5.8 Lithium Interaction

Increases in serum lithium concentrations and lithium toxicity have been reported with concomitant use of valsartan or thiazide diuretics. Monitor lithium levels in patients receiving Exforge HCT and lithium [see *Drug Interactions (7)*].

5.9 Metabolic Imbalances

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.

5.10 Acute Myopia and Secondary Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

In the controlled trial of Exforge HCT, where only the maximum dose (10/320/25 mg) was evaluated, safety data were obtained in 582 patients with hypertension. Adverse reactions have generally been mild and transient in nature and have only infrequently required discontinuation of therapy.

The overall frequency of adverse reactions was similar between men and women, younger (<65 years) and older (≥65 years) patients, and black and white patients. In the active controlled clinical trial, discontinuation because of adverse events occurred in 4.0% of patients treated with Exforge HCT 10/320/25 mg compared to 2.9% of patients treated with valsartan/HCTZ 320/25 mg, 1.6% of patients treated with amlodipine/valsartan 10/320 mg, and 3.4% of patients treated with HCTZ/amlodipine 25/10 mg. The most common reasons for discontinuation of therapy with Exforge HCT were dizziness (1.0%) and hypotension (0.7%).

The most frequent adverse events that occurred in the active controlled clinical trial in at least 2% of patients treated with Exforge HCT are presented in the following table.

| Preferred Term | Aml/Val/HCTZ 10/320/25 mg N=582 n (%) | Val/HCTZ 320/25 mg N=559 n (%) | Aml/Val 10/320 mg N=566 n (%) | HCTZ/Aml 25/10 mg N=561 n (%) |
|----------------|--|---|--|--|
| Dizziness | 48 (8.2) | 40 (7.2) | 14 (2.5) | 23 (4.1) |
| Edema | 38 (6.5) | 8 (1.4) | 65 (11.5) | 63 (11.2) |
| Headache | 30 (5.2) | 31 (5.5) | 30 (5.3) | 40 (7.1) |

| | | | | |
|-----------------|----------|----------|----------|----------|
| Dyspepsia | 13 (2.2) | 5 (0.9) | 6 (1.1) | 2 (0.4) |
| Fatigue | 13 (2.2) | 15 (2.7) | 12 (2.1) | 8 (1.4) |
| Muscle spasms | 13 (2.2) | 7 (1.3) | 7 (1.2) | 5 (0.9) |
| Back pain | 12 (2.1) | 13 (2.3) | 5 (0.9) | 12 (2.1) |
| Nausea | 12 (2.1) | 7 (1.3) | 10 (1.8) | 12 (2.1) |
| Nasopharyngitis | 12 (2.1) | 13 (2.3) | 13 (2.3) | 12 (2.1) |

Orthostatic events (orthostatic hypotension and postural dizziness) were seen in 0.5% of patients.

Valsartan

Valsartan has been evaluated for safety in more than 4000 hypertensive patients in clinical trials. In trials in which valsartan was compared to an ACE inhibitor with or without placebo, the incidence of dry cough was significantly greater in the ACE inhibitor group (7.9%) than in the groups who received valsartan (2.6%) or placebo (1.5%). In a 129-patient trial limited to patients who had dry cough when they had previously received ACE inhibitors, the incidences of cough in patients who received valsartan, HCTZ, or lisinopril were 20%, 19%, and 69% respectively (p <0.001).

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 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.

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. 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 [see *Warnings and Precautions (5.4)*].

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

6.2 Postmarketing Experience

The following additional adverse reactions have been reported in 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.

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 postmarketing experience with valsartan or valsartan/hydrochlorothiazide:

Blood and Lymphatic: Decrease in hemoglobin, decrease in hematocrit, neutropenia

Hypersensitivity: Angioedema has been reported. Some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Exforge HCT should not be re-administered to patients who have had angioedema.

Digestive: Elevated liver enzymes and reports of hepatitis

Musculoskeletal: Rhabdomyolysis

Renal: Impaired renal function, renal failure

Dermatologic: Alopecia, bullous dermatitis

Vascular: Vasculitis

Nervous System: Syncope

Hydrochlorothiazide

The following additional adverse reactions have been reported in postmarketing 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.

7 DRUG INTERACTIONS

No drug interaction studies have been conducted with Exforge HCT and other drugs, although studies have been conducted with the individual components. A pharmacokinetic drug-drug interaction study has been conducted to address the potential for pharmacokinetic interaction between the triple combination, Exforge HCT, and the corresponding 3 double combinations. No clinically relevant interaction was observed.

Amlodipine

Impact of other Drugs on Amlodipine

CYP3A Inhibitors

Coadministration with CYP3A inhibitors (moderate and strong) results in increased systemic exposure to amlodipine and may require dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is coadministered with CYP3A inhibitors to determine the need for dose adjustment [*see Clinical Pharmacology (12.3)*].

CYP3A Inducers

No information is available on the quantitative effects of CYP3A inducers on amlodipine. Blood pressure should be closely monitored when amlodipine is coadministered with CYP3A inducers (e.g., rifampicin, St. John's Wort).

Sildenafil

Monitor for hypotension when sildenafil is coadministered with amlodipine [*see Clinical Pharmacology (12.2)*].

Impact of Amlodipine on Other Drugs

Simvastatin

Coadministration of simvastatin with amlodipine increases the systemic exposure of simvastatin. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily [*see Clinical Pharmacology (12.3)*].

Immunosuppressants

Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when coadministered. Frequent monitoring of trough blood levels of cyclosporine and tacrolimus is recommended and adjust the dose when appropriate [*see Clinical Pharmacology (12.3)*].

Valsartan

Agents Increasing Serum Potassium: Concomitant use of valsartan with other agents that block the renin-angiotensin system, potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, salt substitutes containing potassium or other drugs that may increase potassium levels (e.g., heparin) may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine. If co-medication is considered necessary, monitoring of serum potassium is advisable.

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, coadministration 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.

Dual Blockade of the Renin-Angiotensin System (RAS): Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Most patients receiving the combination of two RAS inhibitors do not obtain any additional benefit compared to monotherapy. In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function and electrolytes in patients on valsartan and other agents that affect the RAS.

Do not coadminister aliskiren with valsartan in patients with diabetes. Avoid use of aliskiren with valsartan in patients with renal impairment (GFR <60 mL/min).

Valsartan – Hydrochlorothiazide

Lithium: Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists or thiazides. Monitor lithium levels in patients taking Exforge HCT.

Hydrochlorothiazide

When administered concurrently the following drugs may interact with thiazide diuretics:

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

Non-Steroidal Anti-inflammatory Drugs (NSAIDs and COX-2 selective inhibitors): 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 to 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Exforge HCT can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-

angiotensin system from other antihypertensive agents. Published reports include cases of anhydramnios and oligohydramnios in pregnant women treated with valsartan (*see Clinical Considerations*).

When pregnancy is detected, discontinue Exforge HCT as soon as possible.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage).

Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

Fetal/Neonatal Adverse Reactions

Valsartan

Oligohydramnios in pregnant women who use drugs affecting the renin-angiotensin system in the second and third trimesters of pregnancy can result in the following: reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension and death.

Perform serial ultrasound examinations to assess the intra-amniotic environment. Fetal testing may be appropriate, based on the week of gestation. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. If oligohydramnios is observed, consider alternative drug treatment. Closely observe neonates with histories of *in utero* exposure to Exforge HCT for hypotension, oliguria, and hyperkalemia. In neonates with a history of *in utero* exposure to Exforge HCT, if oliguria or hypotension occurs, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and replacing renal function.

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 (preeclampsia), these drugs should not be used to treat hypertension in pregnant women. The use of HCTZ for other indications (e.g., heart disease) in pregnancy should be avoided.

Data

Animal Data

Valsartan and Amlodipine

In rats, administered 20 mg/kg/day amlodipine plus 320 mg/kg/day valsartan, treatment-related maternal and fetal effects (developmental delays and alterations noted in the presence of significant maternal toxicity) were noted with the high dose combination. This corresponds to dose multiples of 9 and 19.5 times, respectively, the maximum recommended human dose (MRHD) of 10 mg/day for amlodipine and 320 mg/day for valsartan (based on body surface area and considering a 60 kg patient).

Hydrochlorothiazide

No teratogenic effects were observed when hydrochlorothiazide was administered to mice and rats via gavage at doses of up to 3000 and 1000 mg/kg/day (608 and 405 times the MRHD), on gestation days 6 through 15.

8.2 Lactation

Risk Summary

There is limited information regarding the presence of Exforge HCT in human milk, the effects on the breastfed infant, or the effects on milk production. Hydrochlorothiazide is present in human milk and valsartan is present in rat milk. Limited published studies report that amlodipine is present in human milk. Because of the potential for serious adverse reactions in breastfed infants, advise a nursing woman that breastfeeding is not recommended during treatment with Exforge HCT.

Data

Valsartan was detected in the milk of lactating rats 15 minutes after oral administration of a 3 mg/kg dose.

8.4 Pediatric Use

The safety and effectiveness of Exforge HCT in pediatric patients have not been established.

8.5 Geriatric Use

Amlodipine

Clinical studies of amlodipine besylate tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40% to 60% [see *Clinical Pharmacology (12.3)*]. The recommended starting dose of amlodipine 2.5 mg is not an available strength with Exforge HCT [see *Clinical Studies (14)*].

8.6 Renal Impairment

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

8.7 Hepatic Impairment

Amlodipine

Exposure to amlodipine is increased in patients with hepatic insufficiency. The recommended initial dose of amlodipine in patients with hepatic impairment is 2.5 mg, which is not an available strength with Exforge HCT [see *Clinical Pharmacology (12.3)*].

Valsartan

No dose adjustment is necessary for patients with mild-to-moderate disease. No dosing recommendations can be provided for patients with 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.

10 OVERDOSAGE

Limited data are available related to overdosage in humans. The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur institute supportive treatment.

Amlodipine

Single oral doses of amlodipine maleate equivalent to 40 mg/kg and 100 mg/kg amlodipine in mice and rats, respectively, caused deaths. Single oral doses equivalent to 4 or more mg/kg amlodipine in dogs (11 or more

times the maximum recommended human dose on a mg/m² basis) caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension. In humans, experience with intentional overdosage of amlodipine is limited. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

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

Valsartan

Depressed level of consciousness, circulatory collapse, and shock have been reported.

Valsartan is not removed from the plasma by hemodialysis.

Valsartan was without grossly observable adverse effects at single oral doses up to 2000 mg/kg in rats and up to 1000 mg/kg in marmosets, except for salivation and diarrhea in the rat and vomiting in the marmoset at the highest dose (60 and 31 times, respectively, the MRHD on a mg/m² basis) (Calculations assume an oral dose of 320 mg/day and a 60-kg patient).

Hydrochlorothiazide

The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The most common signs and symptoms observed in patients are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

The oral LD₅₀ of hydrochlorothiazide is greater than 10 g/kg in both mice and rats, 2000 and 4000 times, respectively, the MRHD on a mg/m² basis (Calculations assume an oral dose of 25 mg/day and a 60-kg patient).

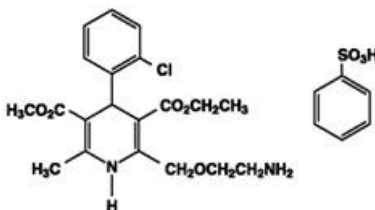
Valsartan and Hydrochlorothiazide

In rats and marmosets, single oral doses of valsartan up to 1524 and 762 mg/kg in combination with hydrochlorothiazide at doses up to 476 and 238 mg/kg, respectively, were very well tolerated without any treatment-related effects. These no adverse effect doses in rats and marmosets, respectively, represent 46.5 and 23 times the MRHD of valsartan and 188 and 113 times the MRHD of hydrochlorothiazide on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60 kg patient.)

11 DESCRIPTION

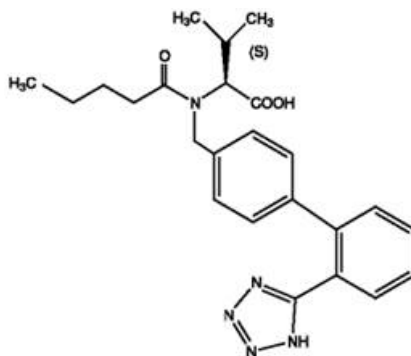
Exforge HCT is a fixed combination of amlodipine, valsartan, and hydrochlorothiazide.

Exforge HCT contains the besylate salt of amlodipine, a dihydropyridine calcium channel blocker (CCB). Amlodipine besylate, USP is a white to pale yellow crystalline powder, slightly soluble in water and sparingly soluble in ethanol. Amlodipine besylate's chemical name is 3-Ethyl 5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(*o*-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulfonate; its structural formula is:



Its empirical formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$ and its molecular weight is 567.1.

Valsartan, USP is a nonpeptide, orally active, and specific angiotensin II antagonist acting on the AT_1 receptor subtype. Valsartan is a white to practically white fine powder, soluble in ethanol and methanol and slightly soluble in water. Valsartan's chemical name is N-(1-oxopentyl)-N-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-L-valine; its structural formula is:

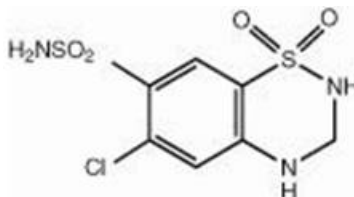


Its empirical formula is $C_{24}H_{29}N_5O_3$ and its molecular weight is 435.5.

Hydrochlorothiazide, USP is a white, or practically white, practically odorless, crystalline powder. It is slightly soluble in water; freely soluble in sodium hydroxide solution, in *n*-butylamine, and in dimethylformamide; sparingly soluble in methanol; and insoluble in ether, in chloroform, and in dilute mineral acids.

Hydrochlorothiazide is chemically described as 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

Hydrochlorothiazide is a thiazide diuretic. Its empirical formula is $C_7H_8ClN_3O_4S_2$, its molecular weight is 297.73, and its structural formula is:



Exforge HCT film-coated tablets are formulated in 5 strengths for oral administration with a combination of amlodipine besylate, valsartan, and hydrochlorothiazide, providing for the following available combinations: 5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg, and 10/320/25 mg amlodipine besylate/valsartan/hydrochlorothiazide. The inactive ingredients for all strengths of the tablets include microcrystalline cellulose; crospovidone; colloidal anhydrous silica; magnesium stearate; hypromellose, macrogol 4000, and talc. Additionally, the 5/160/12.5 mg strength contains titanium dioxide; the 10/160/12.5 mg strength contains titanium dioxide and yellow and red iron oxides; the 5/160/25 mg strength contains titanium dioxide and yellow iron oxide, and the 10/160/25 mg and 10/320/25 mg strengths both contain yellow iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The active ingredients of Exforge HCT target 3 separate mechanisms involved in blood pressure regulation. Specifically, amlodipine blocks the contractile effects of calcium on cardiac and vascular smooth muscle cells; valsartan blocks the vasoconstriction and sodium retaining effects of angiotensin II on cardiac, vascular smooth muscle, adrenal and renal cells; and hydrochlorothiazide directly promotes the excretion of sodium and chloride in the kidney leading to reductions in intravascular volume. A more detailed description of the mechanism of action of each individual component follows.

Amlodipine

Amlodipine is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected *in vitro* but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

Valsartan

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT₁ receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT₂ receptor found in many tissues, but AT₂ is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20000-fold) for the AT₁ receptor than for the AT₂ receptor. The increased plasma levels of angiotensin following AT₁ receptor blockade with valsartan may stimulate the unblocked AT₂ receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT₁ receptor about one-200th that of valsartan itself.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because valsartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of valsartan on blood pressure.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

The mechanism of the antihypertensive effect of thiazides is unknown.

12.2 Pharmacodynamics

Exforge HCT has been shown to be effective in lowering blood pressure. The 3 components of Exforge HCT (amlodipine, valsartan, hydrochlorothiazide) lower the blood pressure through complementary mechanisms, each working at a separate site and blocking different effector pathways. The pharmacodynamics of each individual component are described below.

Exforge HCT has not been studied in indications other than hypertension.

Amlodipine

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic oral administration of amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

With chronic, once-daily administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105-114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90-104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressure (+1/-2 mmHg).

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when coadministered with beta-blockers to man. Similar findings, however, have been observed in normal or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving amlodipine and concomitant beta-blockers. In clinical studies in which amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects of electrocardiographic (ECG) parameters were observed. In clinical trials with angina patients alone, amlodipine therapy did not alter ECG intervals or produce higher degrees of AV blocks.

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

Drug Interactions

Sildenafil

When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect [*see Drug Interactions (7)*].

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.

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.

12.3 Pharmacokinetics

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 to 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 to 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% to 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 biexponential 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 coadministered 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

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 biexponentially, with a mean distribution half-life of about 2 hours and an elimination half-life of about 10 hours.

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

Specific Populations

Geriatric: Elderly patients have decreased clearance of amlodipine with a resulting increase in peak plasma levels, elimination half-life, and AUC. 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 do not differ significantly between males and females.

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

Renal Insufficiency: The pharmacokinetics of amlodipine are 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 ($30 < \text{CrCl} < 90$ mL/min) and tripled in severe renal impairment ($\text{CrCl} \leq 30$ mL/min), compared to individuals with normal renal function ($\text{CrCl} > 90$ mL/min) [see *Use in Specific Populations (8.6)*].

Hepatic Insufficiency: Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40% to 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 Specific Populations (8.7)*].

Drug Interactions

Amlodipine:

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

Impact of other Drugs on Amlodipine

Coadministered cimetidine, magnesium-and aluminum hydroxide antacids, sildenafil, and grapefruit juice have no impact on the exposure to amlodipine.

CYP3A Inhibitors: Coadministration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin coadministration in healthy volunteers did not significantly change amlodipine systemic exposure. However, strong inhibitors of CYP3A (e.g., itraconazole, clarithromycin) may increase the plasma concentrations of amlodipine to a greater extent [see *Drug Interactions (7)*].

Impact of Amlodipine on Other Drugs

Co-administered amlodipine does not affect the exposure to atorvastatin, digoxin, ethanol and the warfarin prothrombin response time.

Simvastatin: Coadministration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone [see *Drug Interactions (7)*].

Cyclosporine: A prospective study in renal transplant patients (N=11) showed on an average of 40% increase in trough cyclosporine levels when concomitantly treated with amlodipine [see *Drug Interactions (7)*].

Tacrolimus: A prospective study in healthy Chinese volunteers (N=9) with CYP3A5 expressers showed a 2.5- to 4-fold increase in tacrolimus exposure when concomitantly administered with amlodipine compared to tacrolimus alone. This finding was not observed in CYP3A5 non-expressers (N=6). However, a 3-fold increase

in plasma exposure to tacrolimus in a renal transplant patient (CYP3A5 non-expressor) upon initiation of amlodipine for the treatment of post-transplant hypertension resulting in reduction of tacrolimus dose has been reported. Irrespective of the CYP3A5 genotype status, the possibility of an interaction cannot be excluded with these drugs [see *Drug Interactions (7)*].

Valsartan

No clinically significant pharmacokinetic interactions were observed when Diovan (valsartan) was coadministered with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. The valsartan-atenolol combination was more antihypertensive than either component, but it did not lower the heart rate more than atenolol alone.

Coadministration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.

Transporters: The results from an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and the hepatic efflux transporter MRP2. Coadministration of inhibitors of the uptake transporter (rifampin, cyclosporine) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.

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, pro-kinetic 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.

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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies with amlodipine/valsartan/hydrochlorothiazide: No carcinogenicity, mutagenicity, or fertility studies have been conducted with this combination. However, these studies have been conducted for amlodipine, valsartan and hydrochlorothiazide alone. Based on the preclinical safety and human pharmacokinetic studies, there is no indication of any toxicologically significant adverse interaction between these components.

Studies with amlodipine: Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg amlodipine/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m² basis, similar to the MRHD of 10 mg amlodipine/day. For the rat, the highest dose was, on a mg/m² basis, about 2.5 times the MRHD. (Calculations based on a 60 kg patient.)

Mutagenicity studies conducted with amlodipine maleate revealed no drug-related effects at either the gene or chromosome level.

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses of up to 10 mg amlodipine/kg/day (about 10 times the MRHD of 10 mg/day on a mg/m² basis).

Studies with valsartan: There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for up to 2 years at concentrations calculated to provide doses of up to 160 and 200 mg/kg/day, respectively. These doses in mice and rats are about 2.4 and 6 times, respectively, the MRHD of 320 mg/day on a mg/m² basis (Calculations based on a 60 kg patient).

Mutagenicity assays did not reveal any valsartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* and *E. coli*, a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with Chinese hamster ovary cells, and a rat micronucleus test.

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses of up to 200 mg/kg/day. This dose is about 6 times the MRHD on a mg/m² basis.

Studies with hydrochlorothiazide: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella Typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and Mouse Lymphoma Cell (mutagenicity) assays and in the *Aspergillus Nidulans* non-disjunction assay.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed via diet at doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation. These doses of hydrochlorothiazide in mice and rats are 19 and 1.5 times, respectively, the MRHD on a mg/m² basis (Calculations assume an oral dose of 25 mg/day and a 60-kg patient).

14 CLINICAL STUDIES

Exforge HCT was studied in a double-blind, active controlled study in hypertensive patients. A total of 2271 patients with moderate to severe hypertension (mean baseline systolic/diastolic blood pressure was 170/107 mmHg) received treatments of amlodipine/valsartan/HCTZ 10/320/25 mg, valsartan/HCTZ 320/25 mg, amlodipine/valsartan 10/320 mg, or HCTZ/amlodipine 25/10 mg. At study initiation, patients assigned to the 2-component arms received lower doses of their treatment combination while patients assigned to the Exforge HCT arm received 160/12.5 mg valsartan/hydrochlorothiazide. After 1 week, Exforge HCT patients were titrated to 5/160/12.5 mg amlodipine/valsartan/hydrochlorothiazide, while all other patients continued receiving their initial doses. After 2 weeks, all patients were titrated to their full treatment dose. A total of 55% of patients were male, 14% were 65 years or older, 72% were Caucasian, and 17% were black.

At Week 8, the triple combination therapy produced greater reductions in blood pressure than each of the 3 dual combination treatments ($p < 0.0001$ for both diastolic and systolic blood pressures reductions). The reductions in systolic/diastolic blood pressure with Exforge HCT were 7.6/5.0 mmHg greater than with valsartan/HCTZ, 6.2/3.3 mmHg greater than with amlodipine/valsartan, and 8.2/5.3 mmHg greater than with amlodipine/HCTZ (see Figure 1). The full blood pressure lowering effect was achieved 2 weeks after being on the maximal dose of Exforge HCT (see Figure 2 and Figure 3). As the pivotal study was an active-controlled trial, the treatment effects shown in Figures 1, 2, and 3 include a placebo effect of unknown size.

Figure 1: Reduction in Mean Blood Pressure at Endpoint

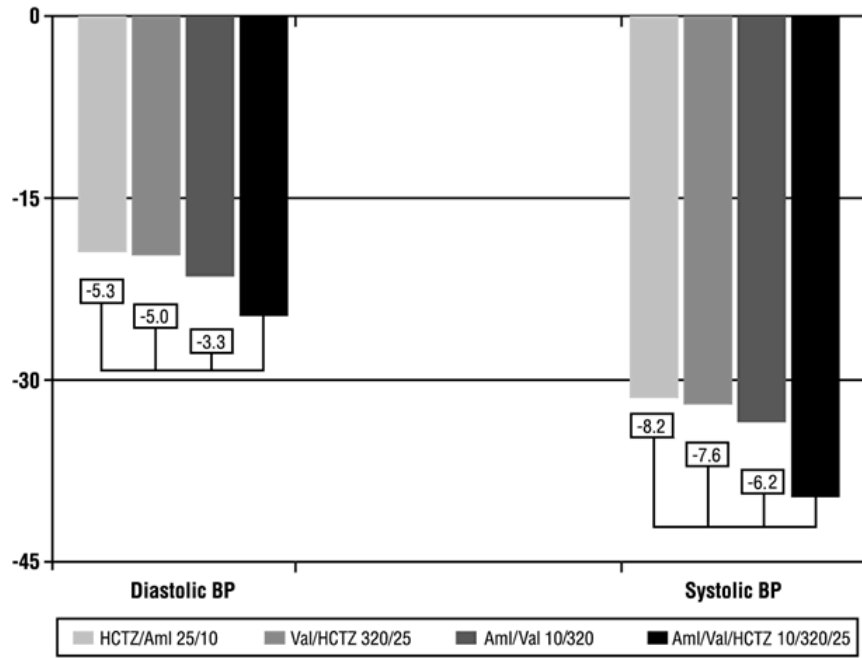


Figure 2: Mean Sitting Diastolic Blood Pressure by Treatment and Week

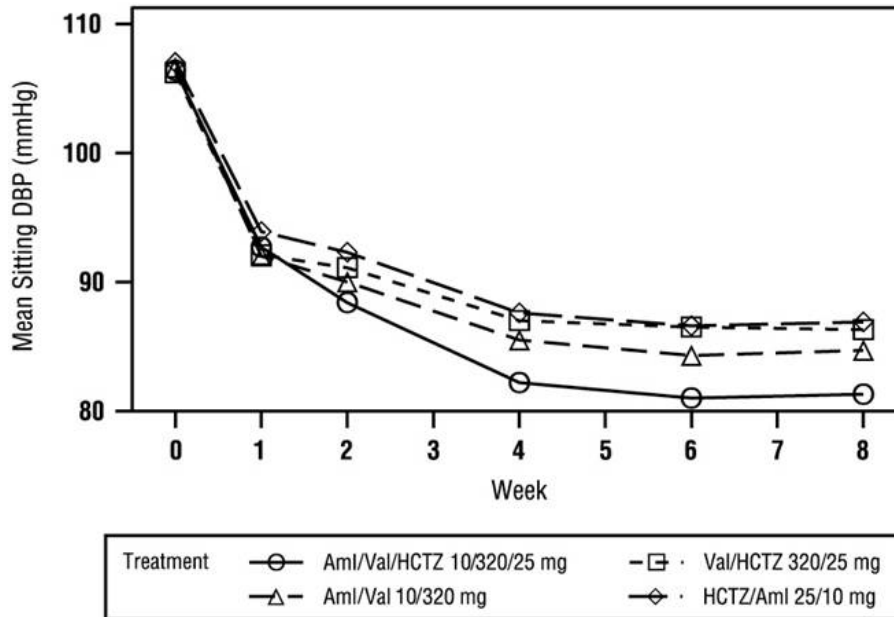
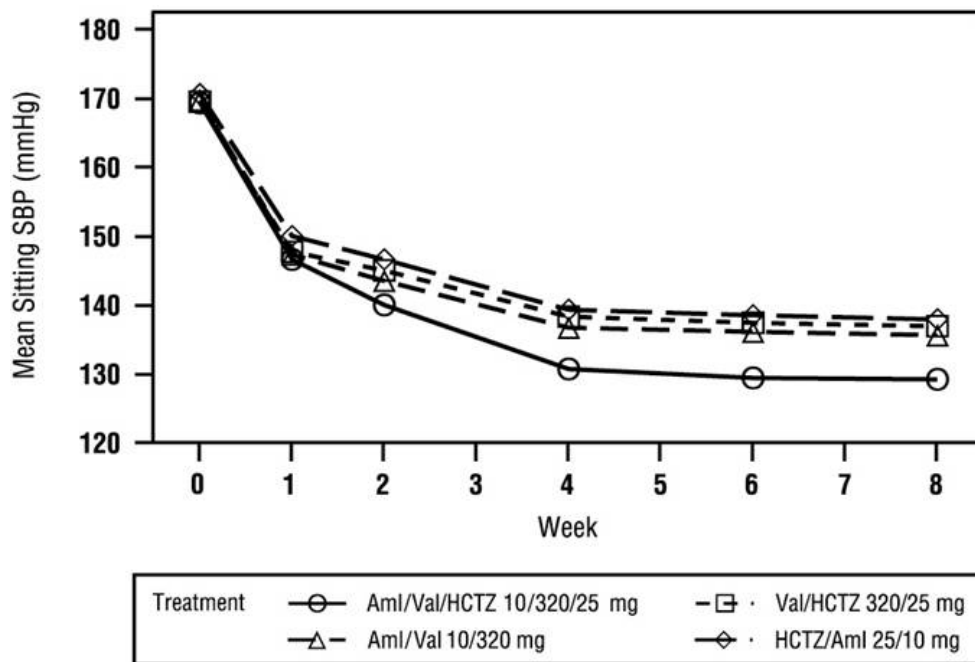


Figure 3: Mean Sitting Systolic Blood Pressure by Treatment and Week



A subgroup of 283 patients was studied with ambulatory blood pressure monitoring. The blood pressure lowering effect in the triple therapy group was maintained throughout the 24-hour period (see Figure 4 and Figure 5).

Figure 4: Mean Ambulatory Diastolic Blood Pressure at Endpoint by Treatment and Hour

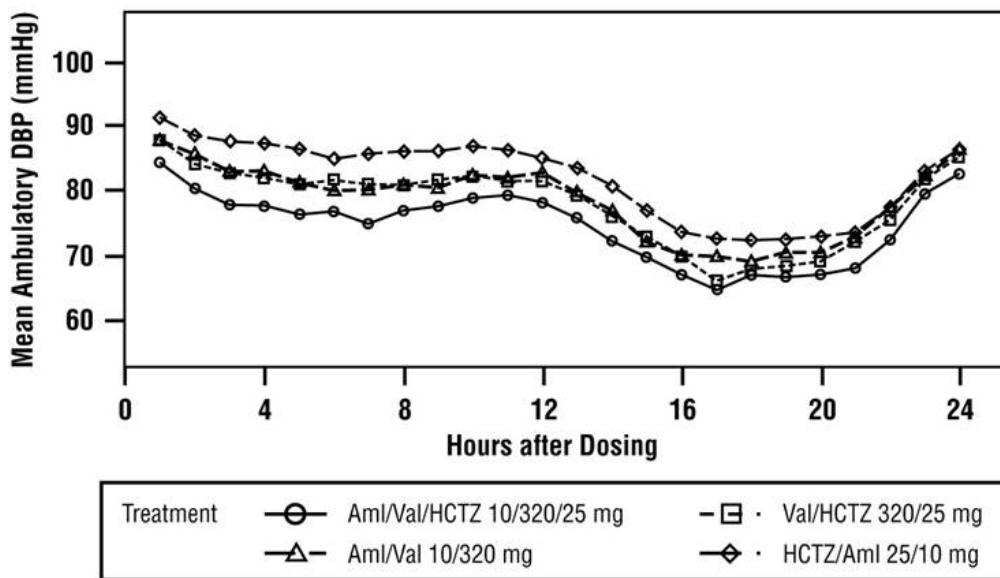
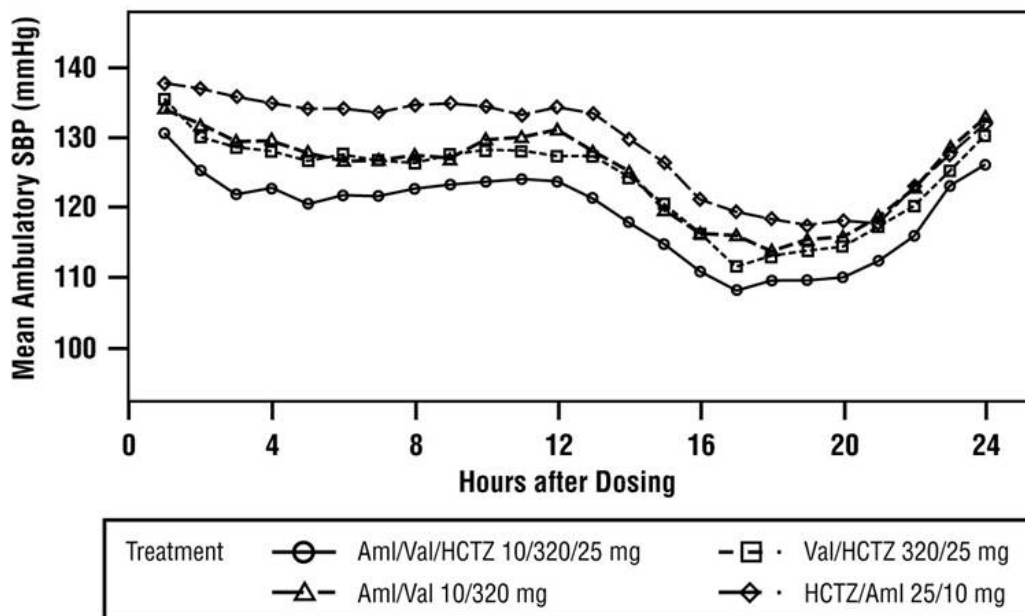


Figure 5: Mean Ambulatory Systolic Blood Pressure at Endpoint by Treatment and Hour



There are no trials of the Exforge HCT combination tablet demonstrating reductions in cardiovascular risk in patients with hypertension, but both the amlodipine and hydrochlorothiazide components and several ARBs, which are the same pharmacological class as the valsartan component, have demonstrated such benefits.

16 HOW SUPPLIED/STORAGE AND HANDLING

Exforge HCT (amlodipine, valsartan, hydrochlorothiazide) is available as film-coated tablets containing amlodipine besylate equivalent to 5 mg or 10 mg of amlodipine free-base with valsartan 160 mg or 320 mg, and hydrochlorothiazide 12.5 mg or 25 mg, providing for the following available combinations: 5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg, and 10/320/25 mg. All strengths are packaged in bottles of 30 tablets.

5 mg amlodipine /160 mg valsartan /12.5 mg hydrochlorothiazide Tablets – White, non-scored, film-coated tablet, ovaloid, biconvex with beveled edge with debossing “NVR” on one side and “VCL” on the other side.

Bottles of 30

NDC 0078-0559-15

10 mg amlodipine /160 mg valsartan /12.5 mg hydrochlorothiazide Tablets – Pale yellow, non-scored, film-coated tablet, ovaloid, biconvex with beveled edge with debossing “NVR” on one side and “VDL” on the other side.

Bottles of 30

NDC 0078-0561-15

5 mg amlodipine /160 mg valsartan /25 mg hydrochlorothiazide Tablets – Yellow, non-scored, film-coated tablet, ovaloid, biconvex with beveled edge with debossing “NVR” on one side and “VEL” on the other side.

Bottles of 30

NDC 0078-0560-15

10 mg amlodipine /160 mg valsartan /25 mg hydrochlorothiazide Tablets – Brown-yellow, non-scored, film-coated tablet, ovaloid, biconvex with beveled edge with debossing “NVR” on one side and “VHL” on the other side.

Bottles of 30

NDC 0078-0562-15

10 mg amlodipine /320 mg valsartan /25 mg hydrochlorothiazide Tablets – Brown-yellow, non-scored, film-coated tablet, ovaloid, biconvex with beveled edge with debossing “NVR” on one side and “VFL” on the other side.

Bottles of 30

NDC 0078-0563-15

Store at 20°C-25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP controlled room temperature].

Protect from moisture.

Dispense in tight container (USP).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Pregnancy: Advise female patients of childbearing age about the consequences of exposure to Exforge HCT during pregnancy. Discuss treatment options with women planning to become pregnant. Ask patients to report pregnancies to their physicians as soon as possible [see *Warnings and Precautions (5.1)* and *Use in Specific Populations (8.1)*]

Lactation: Advise women not to breastfeed during treatment with Exforge HCT [see *Use in Specific Populations (8.2)*].

Symptomatic Hypotension: Advise patients that lightheadedness can occur, especially during the first days of therapy, and that it should be reported to their healthcare provider. Tell patients that if syncope occurs to discontinue Exforge HCT until the physician has been consulted. Caution all patients that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope [see *Warnings and Precautions (5.2)*].

Potassium Supplements: Advise patients not to use salt substitutes without consulting their healthcare provider [see *Drug Interactions (7)*].

Information for Patients

Patient Information

Exforge HCT® (X-phorj HCT)

(amlodipine and valsartan and hydrochlorothiazide) Tablets

Read the Patient Information that comes with EXFORGE HCT before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or treatment.

What is the most important information I should know about EXFORGE HCT?

- EXFORGE HCT can cause harm or death to an unborn baby.
- Talk to your doctor about other ways to lower your blood pressure if you plan to become pregnant.
- If you get pregnant while taking EXFORGE HCT, tell your doctor right away.

What is EXFORGE HCT?

EXFORGE HCT contains 3 prescription medicines:

1. amlodipine, a calcium channel blocker
2. valsartan, an angiotensin receptor blocker, and
3. hydrochlorothiazide, a diuretic (water pill)

EXFORGE HCT may be used to lower blood pressure in adults when 2 medicines to lower your high blood pressure are not enough.

EXFORGE HCT has not been studied in children under 18 years of age.

Who should not take EXFORGE HCT?

Do not take EXFORGE HCT if you have low or no urine output (anuria).

What should I tell my doctor before taking EXFORGE HCT?

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 breastfeeding or plan to breastfeed.** EXFORGE HCT is present in human milk. It is not known whether EXFORGE HCT affects your breastfed baby or milk production. Do not breastfeed 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
- 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.
- have ever had a reaction called angioedema, to another blood pressure medicine. Angioedema causes swelling of the face, lips, tongue, and may cause difficulty breathing.

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:

- simvastatin or other cholesterol-lowering medicine
- other medicines for high blood pressure or a heart problem
- water pills (“diuretics”)
- potassium supplements. Your doctor may check the amount of potassium in your blood periodically.
- salt substitute containing potassium. Your doctor may check the amount of potassium in your blood periodically.
- diabetes medicine including insulin
- narcotic pain medicines
- sleeping pills and antiseizure medicines called barbiturates
- lithium, a medicine used to treat some types of depression
- aspirin or other medicines called nonsteroidal anti-inflammatory drugs (NSAIDs), like ibuprofen or naproxen
- steroids
- alcohol
- digoxin or other digitalis glycosides (a heart medicine)
- muscle relaxants (medicines used during operations)
- certain cancer medicines, like cyclophosphamide or methotrexate
- medicines used to prevent and treat fungal infections (such as ketoconazole, itraconazole)
- medicines used to treat bacterial infections (such as clarithromycin, telithromycin)
- certain antibiotics (rifamycin group), a drug used to protect against transplant rejection (cyclosporine) or an antiretroviral drug used to treat HIV/AIDS infection (ritonavir). These drugs may increase the effect of valsartan.

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.

How should I take EXFORGE HCT?

- Take EXFORGE HCT exactly as your doctor tells you.
- Take EXFORGE HCT one time each day.
- EXFORGE HCT can be taken with or without food.
- If you miss a dose, take it as soon as you remember. If it is close to your next dose, do not take the missed dose. Just take the next dose at the regular time.
- If you take too much EXFORGE HCT, call your doctor or Poison Control Center, or go to the emergency room.
- Tell all your doctors and dentist you are taking EXFORGE HCT. This is especially important if you:
 - are going to have surgery
 - go for kidney dialysis

What are the possible side effects of EXFORGE HCT?

EXFORGE HCT may cause **serious side effects** including:

- **harm to an unborn baby causing injury or death.** See “**What is the most important information I should know about EXFORGE HCT?**”
- **low blood pressure** (hypotension). Low blood pressure is most likely to happen if you:
 - take water pills
 - are on a low-salt diet
 - have heart problems

- get dialysis treatments
- get sick with vomiting or diarrhea
- drink alcohol

Lie down if you feel faint or dizzy. If you faint (lose consciousness), stop taking EXFORGE HCT. Call your doctor right away.

- Get emergency help if you get worse chest pain or chest pain that does not go away.
- **kidney problems.** Kidney problems may become worse in people that already have kidney disease. Some people will have changes in blood tests for kidney function and may need a lower dose of EXFORGE HCT. Call your doctor if you have 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 EXFORGE HCT.
- **laboratory blood test changes in people with heart failure.** Some people with heart failure who take valsartan, one of the medicines in EXFORGE HCT, have changes in blood tests including increased potassium and decreased kidney function.
- **allergic reactions**
- **skin rash.** Call your doctor right away if you get an unusual skin rash.
- **eye problems.** One of the medicines in EXFORGE HCT can cause eye problems that may lead to vision loss. Symptoms of eye problems can happen within hours to weeks of starting EXFORGE HCT. Tell your doctor right away if you have:
 - decrease in vision
 - eye pain

The **most common** side effects of EXFORGE HCT include:

- dizziness
- swelling (edema) of the hands, ankles, or feet
- headache
- indigestion
- tiredness
- muscle spasms
- back pain
- nausea

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 EXFORGE HCT. For more information, 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.

How should I store EXFORGE HCT?

- Store EXFORGE HCT at room temperature between 59°F and 86°F (15°C and 30°C).
- Keep EXFORGE HCT dry (protect it from moisture).

Keep EXFORGE HCT and all medicines out of the reach of children.

General Information about EXFORGE HCT

Medicines are sometimes prescribed for conditions that are not mentioned in the patient information leaflet. Do not use EXFORGE HCT for a condition for which it was not prescribed. Do not give EXFORGE HCT to other people, even if they have the same symptoms that you have. It may harm them.

This patient information leaflet summarizes the most important information about EXFORGE HCT. If you would like more information about EXFORGE HCT, talk with your doctor. You can ask your doctor or pharmacist for information about EXFORGE HCT that is written for health professionals. For more information, go to www.EXFORGE.com or call 1-888-839-3674.

What are the ingredients in EXFORGE HCT?

Active ingredients: amlodipine besylate, valsartan, and hydrochlorothiazide

The inactive ingredients of all strengths of the tablets are crospovidone, magnesium stearate, microcrystalline cellulose, and colloidal anhydrous silica. The film coating contains hypromellose, talc, macrogol 4000, and may contain titanium dioxide or yellow and red iron oxides.

What is high blood pressure (hypertension)?

Blood pressure is the force of blood in your blood vessels when your heart beats and when your heart rests. You have high blood pressure when the force is too much. EXFORGE HCT can help your blood vessels relax so your blood pressure is lower. Medicines that lower blood pressure lower your chance of having a stroke or heart attack.

High blood pressure makes the heart work harder to pump blood throughout the body and causes damage to blood vessels. If high blood pressure is not treated, it can lead to stroke, heart attack, heart failure, kidney failure, and vision problems.

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