

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

Initial U.S. Approval: 2009

WARNING: AVOID USE IN PREGNANCY

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

INDICATIONS AND USAGE

- Exforge HCT is for the treatment of hypertension (1)
- Not indicated for initial therapy

DOSAGE AND ADMINISTRATION

- Dose once-daily
- 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).

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; Hypersensitivity to sulfonamide-derived drugs (4)

WARNINGS AND PRECAUTIONS

- Avoid fetal or neonatal exposure (5.1)

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- Symptomatic hypotension with volume- or salt-depletion. Correct volume-depletion prior to administration (5.2)
- Increased angina and/or myocardial infarction (5.3)
- Avoid in patients with severely impaired hepatic (2.1, 5.4) or renal function (creatinine clearance ≤ 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 (5.8)

ADVERSE REACTIONS

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

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

Hydrochlorothiazide (7):

- Alcohol, barbiturates, narcotics: Potentiation of orthostatic hypotension
- Antidiabetic drugs: Dosage adjustment of antidiabetic may be required
- Cholestyramine and colestipol: Reduced absorption of thiazides
- Corticosteroids, ACTH: Hypokalemia, electrolyte depletion
- Lithium: Reduced renal clearance and high risk of lithium toxicity when used with diuretics. Should not be given with diuretics.
- NSAIDs: Can reduce diuretic, natriuretic and antihypertensive effects of diuretics.

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)

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FULL PRESCRIBING INFORMATION

WARNING: AVOID USE IN PREGNANCY

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

1 INDICATIONS AND USAGE

Exforge HCT (amlodipine, valsartan, hydrochlorothiazide) is indicated for the treatment of hypertension.

This fixed combination drug 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 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)].

2.2 Add-on / Switch Therapy

Exforge HCT may be used for patients not adequately controlled on any two 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.

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

Because of the hydrochlorothiazide component, Exforge HCT is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

5 WARNINGS AND PRECAUTIONS

5.1 Fetal/Neonatal Morbidity and Mortality

Exforge HCT can cause harm to the fetus when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Drugs that act on the renin angiotensin system can cause fetal and neonatal morbidity and mortality when used in pregnancy. In several dozen published cases, ACE inhibitor use during the second and third trimesters of pregnancy was associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death [see *Use in Specific Populations* (8.1)].

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, the patient should be placed in a supine position and, if necessary, given an intravenous infusion of 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

Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration or severity of angina or acute myocardial infarction upon starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

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

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 ≤ 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.

5.6 Heart Failure

Exforge HCT has not been studied in patients with heart failure.

Studies with amlodipine: In general, calcium channel blockers should be used with close monitoring, including close follow-up of fluid status, electrolytes, renal function, and blood pressure in patients with heart failure. Amlodipine (5-10 mg per day) has been studied in a placebo-controlled trial of 1,153 patients with NYHA Class III or IV heart failure on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). Amlodipine has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF.

Studies with valsartan: Some patients with heart failure have developed increases in blood urea nitrogen, serum creatinine, and 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. In the Valsartan Heart Failure Trial, in which 93% of patients were on concomitant ACE inhibitors, treatment was discontinued for elevations in creatinine or potassium (total of 1.0% on valsartan vs. 0.2% on placebo). In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), discontinuation due to various types of renal dysfunction occurred in 1.1% of valsartan-treated patients and 0.8% of captopril-treated patients. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function.

5.7 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.

5.8 Systemic Lupus Erythematosus

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

5.9 Lithium Interaction

Lithium generally should not be given with thiazides [see *Drug Interactions, Hydrochlorothiazide, Lithium* (7)].

5.10 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

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.

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 table below:

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.

Other adverse reactions that occurred in clinical trials with Exforge HCT (>0.2%) are listed below. It cannot be determined whether these events were causally related to Exforge HCT.

Cardiac Disorders: tachycardia

Ear and Labyrinth Disorders: vertigo, tinnitus

Eye Disorders: vision blurred

Gastrointestinal Disorders: diarrhea, abdominal pain upper, vomiting, abdominal pain, toothache, dry mouth, gastritis, hemorrhoids

General Disorders and Administration Site Conditions: asthenia, non-cardiac chest pain, chills, malaise

Infections and Infestations: upper respiratory tract infection, bronchitis, influenza, pharyngitis, tooth abscess, gastroenteritis viral, respiratory tract infection, rhinitis, urinary tract infection

Injury, Poisoning and Procedural Complications: back injury, contusion, joint sprain, procedural pain

Investigations: blood uric acid increased, blood creatine phosphokinase increased, weight decreased

Metabolism and Nutrition Disorders: hypokalaemia, diabetes mellitus, hyperlipidemia, hyponatremia

Musculoskeletal and Connective Tissue Disorders: pain in extremity, arthralgia, musculoskeletal pain, muscular weakness, musculoskeletal weakness, musculoskeletal stiffness, joint swelling, neck pain, osteoarthritis, tendonitis

Nervous System Disorders: paraesthesia, somnolence, syncope, carpal tunnel syndrome, disturbance in attention, dizziness postural, dysgeusia, head discomfort, lethargy, sinus headache, tremor

Psychiatric Disorders: anxiety, depression, insomnia

Renal and Urinary Disorders: pollakiuria

Reproductive System and Breast Disorders: erectile dysfunction

Respiratory, Thoracic and Mediastinal Disorders: dyspnea, nasal congestion, cough, pharyngolaryngeal pain

Skin and Subcutaneous Tissue Disorders: pruritus, hyperhidrosis, night sweats, rash

Vascular Disorders: hypotension

Isolated cases of the following clinically notable adverse reactions were also observed in clinical trials: anorexia, constipation, dehydration, dysuria, increased appetite, viral infection.

Amlodipine

Amlodipine has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. Other adverse reactions not listed above that have been reported in <1% but >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain were:

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, peripheral ischemia, syncope, postural hypotension, vasculitis

Central and Peripheral Nervous System: neuropathy peripheral, tremor

Gastrointestinal: anorexia, dysphagia, pancreatitis, gingival hyperplasia

General: allergic reaction, hot flushes, malaise, rigors, weight gain

Musculoskeletal System: arthrosis, muscle cramps

Psychiatric: sexual dysfunction (male and female), nervousness, abnormal dreams, depersonalization

Skin and Appendages: angioedema, erythema multiforme, rash erythematous, rash maculopapular

Special Senses: abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus

Urinary System: micturation frequency, micturation disorder, nocturia

Autonomic Nervous System: sweating increased

Metabolic and Nutritional: hyperglycemia, thirst

Hemopoietic: leukopenia, purpura, thrombocytopenia

Other adverse reactions reported with amlodipine at a frequency of $\leq 0.1\%$ of patients include: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia. Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina.

Adverse reactions reported for amlodipine for indications other than hypertension may be found in its full prescribing information.

Valsartan

Valsartan has been evaluated for safety in more than 4,000 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 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 ($p < 0.001$).

Other adverse reactions, not listed above, occurring in >0.2% of patients in controlled clinical trials with valsartan are:

Digestive: flatulence

Respiratory: sinusitis, pharyngitis

Urogenital: impotence

Adverse reactions reported for valsartan for indications other than hypertension may be found in the prescribing information for Diovan.

Hydrochlorothiazide

Other adverse reactions not listed above that have been reported with hydrochlorothiazide, without regard to causality, are listed below:

Body as a Whole: weakness

Digestive: pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation

Hematologic: aplastic anemia, agranulocytosis, hemolytic anemia

Hypersensitivity: photosensitivity, urticaria, necrotizing angitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions

Metabolic: glycosuria, hyperuricemia

Nervous System/Psychiatric: restlessness

Renal: renal failure, renal dysfunction, interstitial nephritis

Skin: erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis

Special Senses: transient blurred vision, xanthopsia.

6.2 Post-Marketing Experience

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.

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 three double combinations. No clinically relevant interaction was observed.

Amlodipine

In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

Cimetidine: Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

Grapefruit juice: Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

Magnesium and aluminum hydroxide (antacid): Co-administration of the magnesium and aluminum hydroxide antacid with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil: A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Atorvastatin: Co-administration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

Digoxin: Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

Warfarin: Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

Valsartan

No clinically significant pharmacokinetic interactions were observed when valsartan was co-administered 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.

In vitro metabolism studies have indicated that CYP450 mediated drug interaction between valsartan and co-administered drugs are unlikely because of the low extent of metabolism [see *Pharmacokinetics - Valsartan*, 12.3].

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

As with other drugs that block angiotensin II or its effects, concomitant use of potassium sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine.

Hydrochlorothiazide

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

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

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

Other antihypertensive drugs: Additive effect or potentiation.

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

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia.

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

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

Lithium: Should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with Exforge HCT.

Non-steroidal anti-inflammatory drugs: 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.

Carbamazepine: May lead to symptomatic hyponatremia.

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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

Valsartan, like other drugs that act on the renin angiotensin system, can cause fetal and neonatal morbidity and death when used during the second or third trimester of pregnancy. If Exforge HCT is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Angiotensin II receptor antagonists, like valsartan, and angiotensin converting enzyme (ACE) inhibitors exert similar effects on the renin-angiotensin system. In several dozen published cases, ACE inhibitor use during the second and third trimesters of pregnancy was associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios was also reported, presumably from decreased fetal renal function. In this setting, oligohydramnios was associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus were also reported, although it is not clear whether these occurrences were due to exposure to the drug. In a retrospective study, first trimester use of ACE inhibitors, a specific class of drugs acting on the renin angiotensin system, was associated with a potential risk of birth defects.

When pregnancy occurs in a patient using Exforge HCT, the physician should discontinue Exforge HCT treatment as soon as possible. The physician should inform the patient about potential risks to the fetus based on the time of gestational exposure to Exforge HCT (first trimester only or later). If exposure occurs beyond the first trimester, an ultrasound examination should be done.

In rare cases when another antihypertensive agent can not be used to treat the pregnant patient, serial ultrasound examinations should be performed to assess the intraamniotic environment. Routine fetal testing with non-stress tests, biophysical profiles, and/or contraction stress tests may be appropriate based on gestational age and standards of care in the community. If oligohydramnios occurs in these situations, individualized decisions about continuing or discontinuing Exforge HCT treatment and about pregnancy management should be made by the patient, her physician, and experts in the management of high risk pregnancy. Patients and physicians should be aware that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to Exforge HCT should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, these infants may require blood pressure and renal perfusion support. Exchange transfusion or dialysis may be required to reverse hypotension and/or support decreased renal function.

Healthcare professionals who prescribe drugs acting directly on the renin angiotensin system should counsel women of childbearing potential about the risks of these agents during pregnancy. [see *Nonclinical Toxicology* (13.3)].

8.3 Nursing Mothers

It is not known whether amlodipine and valsartan are excreted in human milk, but thiazides are excreted in human milk and valsartan is excreted in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

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

8.5 Geriatric Use

In controlled clinical trials, 82 hypertensive patients treated with Exforge HCT were ≥ 65 years and 13 were ≥ 75 years. No overall differences in the efficacy or safety of Exforge HCT were observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out.

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, supportive treatment should be instituted.

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.

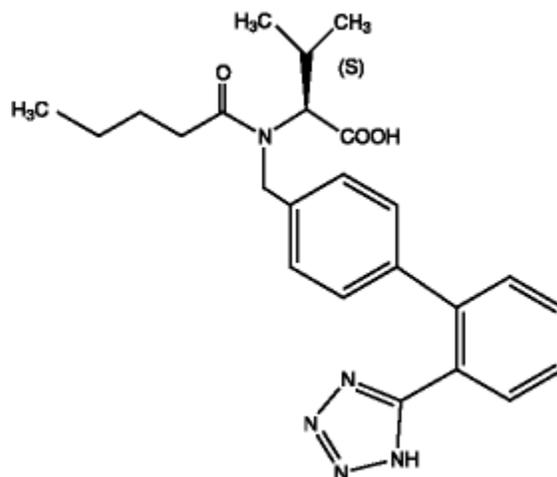
Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension. In humans, experience with intentional overdosage of amlodipine is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) who was hospitalized underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A case of accidental drug overdose has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted.

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

Valsartan

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

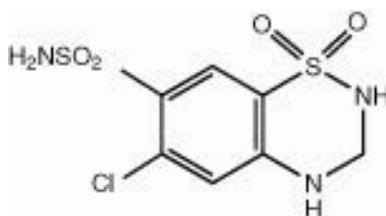
Valsartan is not removed from the plasma by hemodialysis.



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 five 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 three 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 ($pK_a=8.6$), 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 AT_1 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 AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT_1 receptor than for the AT_2 receptor. The increased plasma levels of angiotensin following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT_1 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 three 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 is 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 co-administered with beta-blockers to man. Similar findings, however, have been observed in normals 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 parameters were observed. In clinical trials with angina patients alone, amlodipine therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

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

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.

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.

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.

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 mg/m² basis, similar to the maximum recommended human dose [MRHD] of 10 mg amlodipine/day. For the rat, the highest dose was, on a mg/m² basis, about two and a half 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 maximum recommended human dose 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 maximum recommended human dose on a mg/m² basis. (Calculations assume an oral dose of 25 mg/day and a 60-kg patient.)

13.3 Developmental Toxicity

Studies with amlodipine: No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses of up to 10 mg amlodipine/kg/day (respectively, about 10 and 20 times the maximum recommended human dose [MRHD] of 10 mg amlodipine on a mg/m² basis) during their respective periods of major organogenesis. (Calculations based on a patient weight of 60 kg.) However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) for rats receiving amlodipine maleate at a dose equivalent to 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose. There are no adequate and well controlled studies in pregnant women.

Studies with valsartan: No teratogenic effects were observed when valsartan was administered to pregnant mice and rats at oral doses of up to 600 mg/kg/day and to pregnant rabbits at oral doses of up to 10 mg/kg/day. However, significant decreases in fetal weight, pup birth weight, pup survival rate, and slight delays in developmental milestones were observed in studies in which parental rats were treated with valsartan at oral, maternally toxic (reduction in body weight gain and food consumption) doses of 600 mg/kg/day during organogenesis or late gestation and lactation. In rabbits, fetotoxicity (i.e., resorptions, litter loss, abortions, and low body weight) associated with maternal toxicity (mortality) was observed at doses of 5 and 10 mg/kg/day. The no observed adverse effect doses of 600, 200 and 2 mg/kg/day in mice, rats and rabbits, respectively, are about 9, 6 and 0.1 times the MRHD of 320 mg/day on a mg/m² basis. (Calculations based on a patient weight of 60 kg.)

Studies with hydrochlorothiazide: Under the auspices of the National Toxicology Program, pregnant mice and rats that received hydrochlorothiazide via gavage at doses up to 3000 and 1000 mg/kg/day, respectively, on gestation days 6 through 15 showed no evidence of teratogenicity. These doses of hydrochlorothiazide in mice and rats are 608 and 405 times, respectively, the maximum recommended human dose on a mg/m² basis. (Calculations assume an oral dose of 25 mg/day and a 60-kg patient.)

Studies with amlodipine and valsartan: In the oral embryo-fetal development study in rats using amlodipine besylate plus valsartan at doses equivalent to 5 mg/kg/day amlodipine plus 80 mg/kg/day valsartan, 10 mg/kg/day amlodipine plus 160 mg/kg/day valsartan, and 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. The no-observed-adverse-effect level (NOAEL) for embryo- fetal effects was 10 mg/kg/day amlodipine plus 160 mg/kg/day valsartan. On a systemic exposure [AUC_(0-∞)] basis, these doses are, respectively, 4.3 and 2.7 times the systemic exposure [AUC_(0-∞)] in humans receiving the MRHD (10/320 mg/60 kg).

Studies with valsartan and hydrochlorothiazide: There was no evidence of teratogenicity in mice, rats, or rabbits treated orally with valsartan at doses up to 600, 100 and 10 mg/kg/day, respectively, in combination with hydrochlorothiazide at doses up to 188, 31 and 3 mg/kg/day. These non-teratogenic doses in mice, rats and rabbits are, respectively, 9, 3.5 and 0.5 times the maximum recommended human dose (MRHD) of valsartan and 38, 13 and 2 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 in a 60-kg patient.)

Fetotoxicity was observed in association with maternal toxicity in rats at valsartan/hydrochlorothiazide doses ≥200/63 mg/kg/day and in rabbits at valsartan/hydrochlorothiazide doses of 10/3 mg/kg/day. Evidence of fetotoxicity in rats consisted of decreased fetal weight and fetal variations of sternbrae, vertebrae, ribs and/or renal papillae. Evidence of fetotoxicity in rabbits included increased numbers of late resorptions with resultant increases in total resorptions, postimplantation losses and decreased number of live fetuses. The no observed adverse effect doses of the valsartan/hydrochlorothiazide combination in mice, rats and rabbits were 600/188,

100/31 and 3/1 mg/kg/day, respectively. These doses in mice, rats and rabbits are, respectively, 9, 3 and 0.18 times the MRHD of valsartan and 38, 13 and 0.5 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 in a 60-kg patient.)

14 CLINICAL STUDIES

Exforge HCT was studied in a double-blind, active controlled study in hypertensive patients. A total of 2,271 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 two-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 one 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 two 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 three 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 Figure 1, 2, and 3 include a placebo effect of unknown size.

Figure 1: Reduction in Mean Blood Pressure at Endpoint

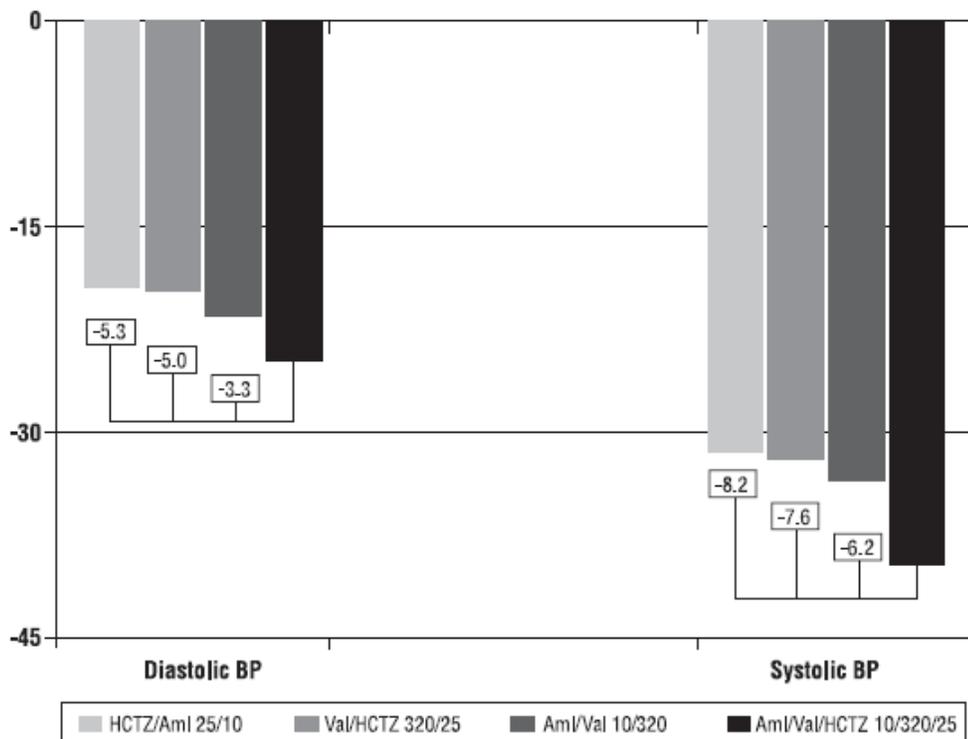


Figure 2: Mean Sitting Diastolic Blood Pressure by Treatment and Week

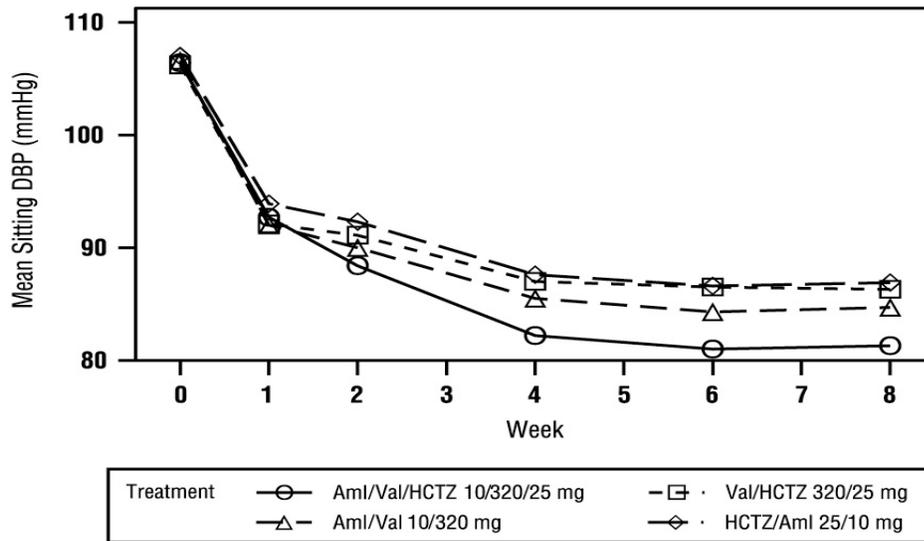
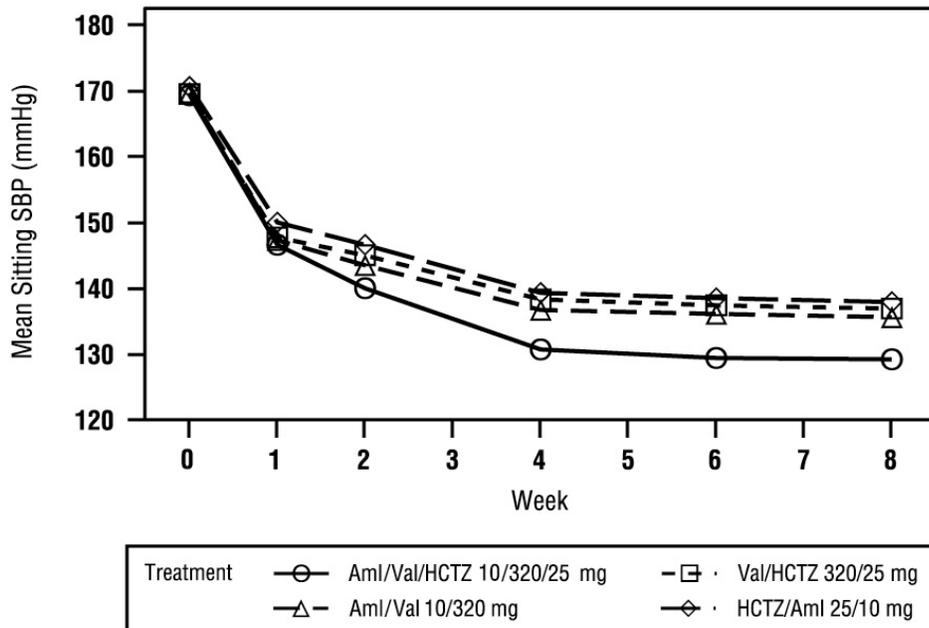


Figure 3: Mean Sitting Systolic Blood Pressure by Treatment and Week



A subgroup of 268 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

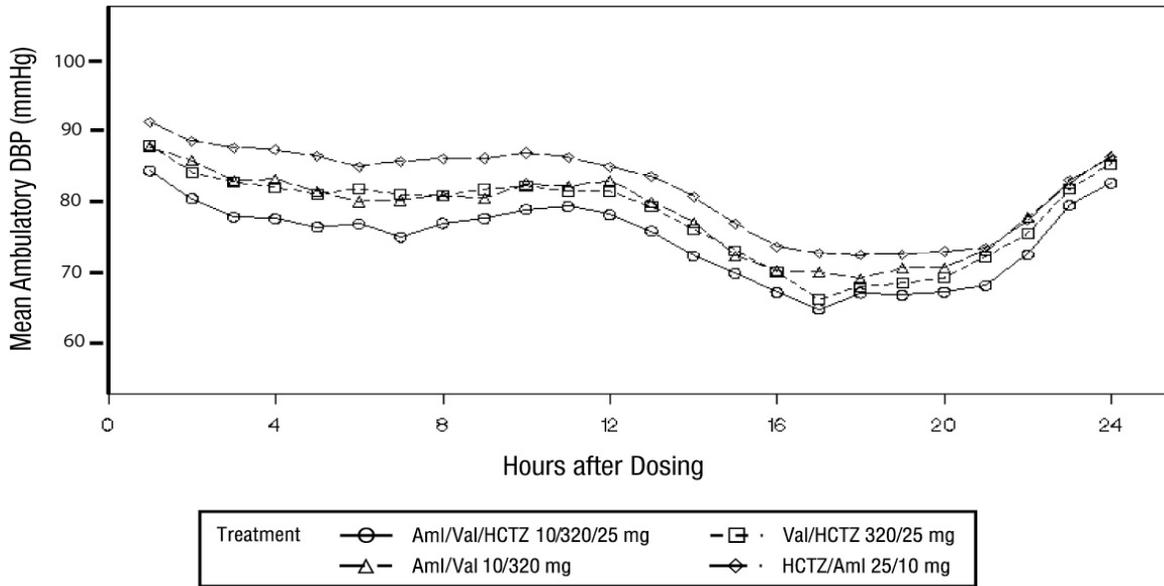
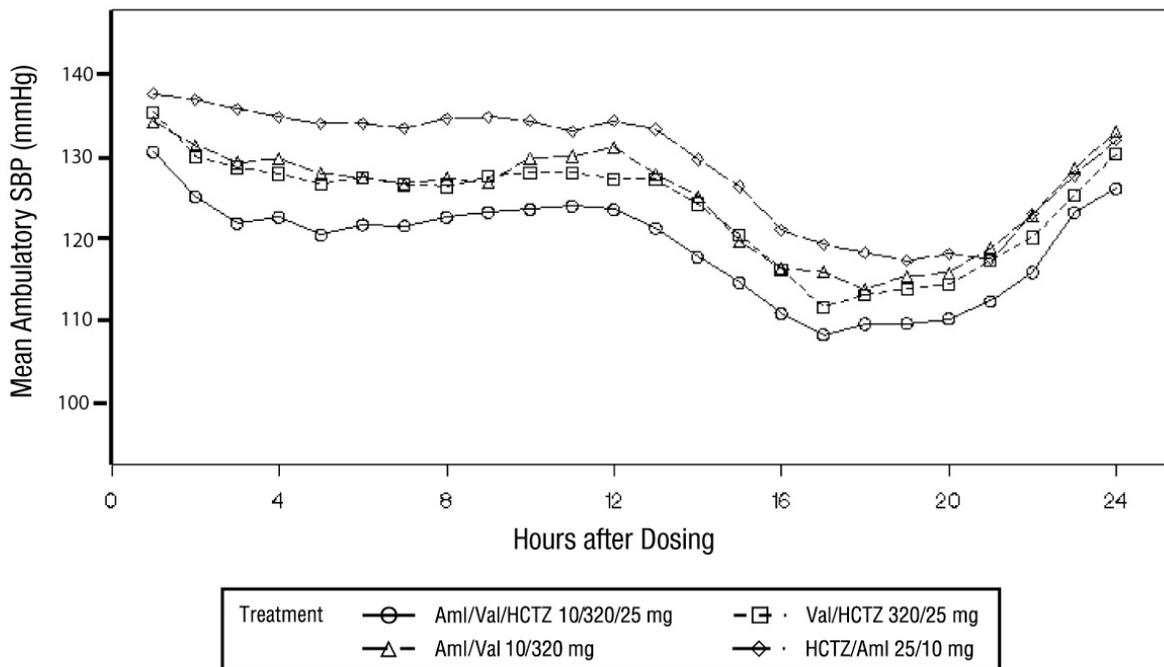


Figure 5: Mean Ambulatory Systolic Blood Pressure at Endpoint by Treatment and Hour



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 and 90 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

Bottles of 90 NDC 0078-0559-34

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

Bottles of 90 NDC 0078-0561-34

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

Bottles of 90 NDC 0078-0560-34

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
Bottles of 90	NDC 0078-0562-34

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
Bottles of 90	NDC 0078-0563-34

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

[see USP controlled room temperature.]

Protect from moisture.

Dispense in tight container (USP).

17 PATIENT COUNSELING INFORMATION

Pregnancy: Female patients of childbearing age should be told that use of drugs like Exforge HCT that act on the renin-angiotensin system during pregnancy can cause serious problems in the fetus and infant including: low blood pressure, poor development of skull bones, kidney failure and death. Discuss other treatment options with female patients planning to become pregnant. Women using Exforge HCT who become pregnant should notify their physician as soon as possible.

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

All patients should be cautioned that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Potassium Supplements: A patient receiving Exforge HCT should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician.

17.1 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?

If you become pregnant while taking EXFORGE HCT, stop taking EXFORGE HCT and call your doctor right away. EXFORGE HCT can harm an unborn baby causing injury or death. Talk to your doctor about other treatment options to lower your blood pressure before taking EXFORGE HCT if you plan to become pregnant.

What is EXFORGE HCT?

EXFORGE HCT contains three 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 two 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 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

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)
- steroids
- cholesterol lowering medicine
- alcohol

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 congestive heart failure.** Some people with congestive 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.

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 to 86°F (15°C to 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. Drugs 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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