

Exforge[®]

(amlodipine and valsartan)

Tablets

Rx only

Prescribing Information

USE IN PREGNANCY

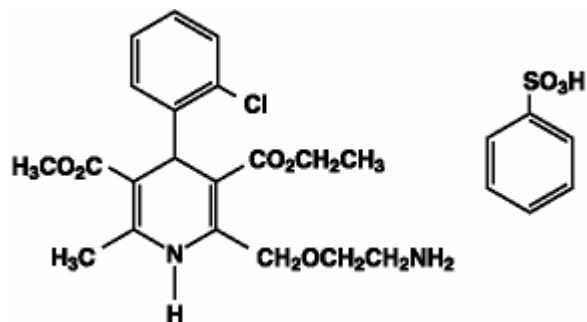
When used in pregnancy, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Exforge[®] (amlodipine and valsartan) should be discontinued as soon as possible.

See **WARNINGS: Fetal/Neonatal Morbidity and Mortality**

DESCRIPTION

Exforge[®] (amlodipine and valsartan) is a fixed combination of amlodipine and valsartan.

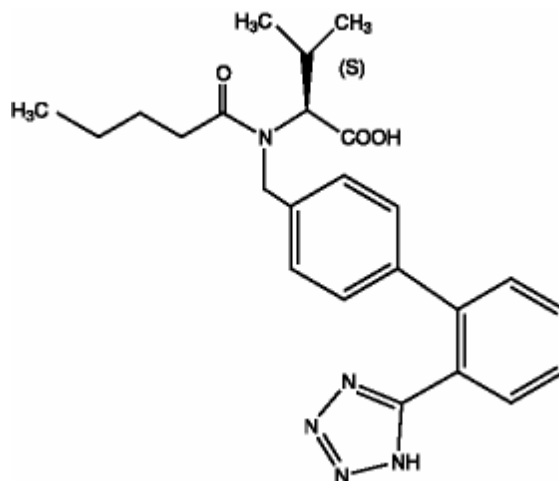
Exforge[®] contains the besylate salt of amlodipine, a dihydropyridine calcium channel blocker (CCB). Amlodipine besylate is a white to pale yellow crystalline powder, slightly soluble in water and sparingly soluble in ethanol. Amlodipine besylate's chemical name is 3-Ethyl-5-methyl (4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-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



Its empirical formula is C₂₀H₂₅ClN₂O₅•C₆H₆O₃S and its molecular weight is 567.1.

Valsartan is a nonpeptide, orally active, and specific angiotensin II antagonist acting on the AT₁ 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'-(1H-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.

Exforge[®] tablets are formulated in four strengths for oral administration with a combination of amlodipine besylate, equivalent to 5 mg or 10 mg of amlodipine free-base, with 160 mg, or 320 mg of valsartan providing for the following available combinations: 5/160 mg, 10/160 mg, 5/320 mg, and 10/320 mg.

The inactive ingredients for all strengths of the tablets are colloidal silicon dioxide, crospovidone, magnesium stearate and microcrystalline cellulose. Additionally the 5/320 mg and 10/320 mg strengths contain iron oxide yellow and sodium starch glycolate. The film coating contains hypromellose, iron oxides, polyethylene glycol, talc and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

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 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 20,000-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.

Pharmacokinetics

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 bioavailability of amlodipine is not altered by the presence of food.

The apparent volume of distribution of amlodipine is 21 L. 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%). Food decreases the exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%.

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. The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isoenzymes.

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).

Exforge

Following oral administration of Exforge[®] (amlodipine and valsartan) in normal healthy adults, peak plasma concentrations of valsartan and amlodipine are reached in 3 and 6-8 hours, respectively. The rate and extent of absorption of valsartan and amlodipine from Exforge are the same as when administered as individual tablets.

Special Populations

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.

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.

Pharmacodynamics

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 can be found in the Norvasc® package insert.

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 can be found in the Diovan® package insert.

Exforge

Exforge® (amlodipine and valsartan) has been shown to be effective in lowering blood pressure. Both amlodipine and valsartan lower blood pressure by reducing peripheral resistance, but calcium influx blockade and reduction of angiotensin II vasoconstriction are complementary mechanisms.

Exforge has not been studied in indications other than hypertension.

CLINICAL STUDIES

Exforge was studied in 2 placebo-controlled and 2 active-controlled trials in hypertensive patients. In a double-blind, placebo controlled study, a total of 1018 patients with mild to moderate hypertension received treatments of three combinations of amlodipine and valsartan (5/80, 5/160, 5/320 mg), or amlodipine alone (5 mg), valsartan alone (80, 160, or 320 mg) or

placebo. At week 8, the combination treatments were statistically significantly superior to their monotherapy components in reduction of diastolic and systolic blood pressures.

Effect of Exforge on Sitting Diastolic Blood Pressure

Amlodipine dosage	Valsartan dosage							
	0 mg		80 mg		160 mg		320 mg	
	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted
0 mg	-6.4	---	-9.5	-3.1	-10.9	-4.5	-13.2	-6.7
5 mg	-11.1	-4.7	-14.2	-7.8	-14.0	-7.6	-15.7	-9.3

*Mean Change and Placebo-Subtracted Mean Change from Baseline (mmHg) at Week 8 in Sitting Diastolic Blood Pressure. Mean baseline diastolic BP was 99.3 mmHg.

Effect of Exforge on Sitting Systolic Blood Pressure

Amlodipine dosage	Valsartan dosage							
	0 mg		80 mg		160 mg		320 mg	
	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted
0 mg	-6.2	---	-12.9	-6.8	-14.3	-8.2	-16.3	-10.1
5 mg	-14.8	-8.6	-20.7	-14.5	-19.4	-13.2	-22.4	-16.2

*Mean Change and Placebo-Subtracted Mean Change from Baseline (mmHg) at Week 8 in Sitting Systolic Blood Pressure. Mean baseline systolic BP was 152.8 mmHg.

In a double-blind, placebo controlled study, a total of 1250 patients with mild to moderate hypertension received treatments of two combinations of amlodipine and valsartan (10/160, 10/320 mg), or amlodipine alone (10 mg), valsartan alone (160 or 320 mg) or placebo. At week 8, the combination treatments were statistically significantly superior to their monotherapy components in reduction of diastolic and systolic blood pressures.

Effect of Exforge on Sitting Diastolic Blood Pressure

Amlodipine dosage	Valsartan dosage					
	0 mg		160 mg		320 mg	
	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted
0 mg	-8.2	---	-12.8	- 4.5	-12.8	-4.5
10 mg	-15.0	-6.7	- 17.2	- 9.0	-18.1	-9.9

*Mean Change and Placebo-Subtracted Mean Change from Baseline (mmHg) at Week 8 in Sitting Diastolic Blood Pressure. Mean baseline diastolic BP was 99.1 mmHg.

Effect of Exforge on Sitting Systolic Blood Pressure

Amlodipine dosage	Valsartan dosage					
	0 mg		160 mg		320 mg	
	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted
0 mg	-11.0	---	-18.1	-7.0	-18.5	-7.5
10 mg	-22.2	-11.2	-26.6	-15.5	-26.9	-15.9

*Mean Change and Placebo-Subtracted Mean Change from Baseline (mmHg) at Week 8 in Sitting Systolic Blood Pressure. Mean baseline systolic BP was 156.7 mmHg.

In a double-blind, active-controlled study, a total of 947 patients with mild to moderate hypertension who were not adequately controlled on valsartan 160 mg received treatments of two combinations of amlodipine and valsartan (10/160, 5/160 mg), or valsartan alone (160 mg). At week 8, the combination treatments were statistically significantly superior to the monotherapy component in reduction of diastolic and systolic blood pressures.

Effect of Exforge on Sitting Diastolic/Systolic Blood Pressure

Treatment Group	Diastolic BP		Systolic BP	
	Mean change*	Treatment Difference**	Mean change*	Treatment Difference**
Exforge 10/160 mg	-11.4	-4.8	-13.9	-5.7
Exforge 5/160 mg	-9.6	-3.1	-12.0	-3.9
Valsartan 160 mg	-6.6	---	-8.2	---

*Mean Change from Baseline at Week 8 in Sitting Diastolic/Systolic Blood Pressure. Mean baseline BP was 149.5/ 96.5 (systolic/diastolic) mmHg

**Treatment Difference = difference in mean BP reduction between Exforge and the control group (Valsartan 160 mg)

In a double-blind, active-controlled study, a total of 944 patients with mild to moderate hypertension who were not adequately controlled on amlodipine 10 mg received a combination of amlodipine and valsartan (10/160 mg), or amlodipine alone (10 mg). At week 8, the combination treatment was statistically significantly superior to the monotherapy component in reduction of diastolic and systolic blood pressures.

Effect of Exforge on Sitting Diastolic/Systolic Blood Pressure

Treatment Group	Diastolic BP		Systolic BP	
	Mean change*	Treatment Difference**	Mean change*	Treatment Difference**
Exforge 10/160 mg	-11.8	-1.8	-12.7	-1.9
Amlodipine 10 mg	-10.0	---	-10.8	---

*Mean Change from Baseline at Week 8 in Sitting Diastolic/Systolic Blood Pressure. Mean baseline BP was 147.0/ 95.1 (systolic/diastolic) mmHg

**Treatment Difference = difference in mean BP reduction between Exforge and the control group (Amlodipine 10 mg)

Exforge was also evaluated for safety in a 6-week, double-blind, active-controlled trial of 130 hypertensive patients with severe hypertension (mean baseline BP of 171/113 mmHg). Adverse events were similar in patients with severe hypertension and mild/moderate hypertension treated with Exforge.

A wide age range of the adult population, including the elderly was studied (range 19-92 years, mean 54.7 years). Women comprised almost half of the studied population (47.3%). Of the patients in the studied Exforge group, 87.6% were Caucasian. Black and Oriental patients each represented approximately 4% of the population in the studied Exforge group.

INDICATIONS AND USAGE

Exforge[®] (amlodipine and valsartan) is indicated[®] for the treatment of hypertension.

This fixed combination drug is not indicated for the initial therapy of hypertension (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Exforge[®] (amlodipine and valsartan) is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction when pregnant women have taken valsartan. When pregnancy is detected, valsartan should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

In addition, first trimester use of ACE inhibitors, a specific class of drugs acting on the renin-angiotensin system, has been associated with a potential risk of birth defects in retrospective data. Healthcare professionals that prescribe drugs acting directly on the renin-angiotensin system should counsel women of childbearing potential about the potential risks of these agents during pregnancy.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should

be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, valsartan should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Hypotension

Excessive hypotension was seen in 0.4% of patients with uncomplicated hypertension treated with Exforge[®] (amlodipine and valsartan) in placebo-controlled studies. In patients with an activated renin-angiotensin system, such as volume-and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur in patients receiving angiotensin receptor blockers. This condition should be corrected prior to administration of Exforge, or the treatment should start under close medical supervision.

Caution should be observed when initiating therapy in patients with heart failure or recent myocardial infarction and 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. Nonetheless, caution, as with any other peripheral vasodilator, should be exercised when administering amlodipine, particularly in patients with severe aortic stenosis.

If excessive hypotension occurs with Exforge, 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.

Increased Angina and/or Myocardial Infarction

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

PRECAUTIONS

General

Impaired Hepatic Function

Studies with amlodipine: Amlodipine is extensively metabolized by the liver and the plasma elimination half-life ($t_{1/2}$) is 56 hours in patients with impaired hepatic function, therefore, caution should be exercised when administering amlodipine to patients with severe hepatic impairment.

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

Impaired Renal Function – Hypertension

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.

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.

Congestive Heart Failure

Studies with amlodipine: In general, calcium channel blockers should be used with caution in patients with heart failure. Amlodipine (5-10 mg per day) has been studied in a placebo-controlled trial of 1153 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.

Beta-Blocker Withdrawal

Amlodipine is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.

Information for Patients

Pregnancy

Female patients of childbearing age should be told about the consequences of exposure to drugs that act on the renin-angiotensin system. Discuss other treatment options with female patients planning to become pregnant. Patients should be asked to report pregnancies to their physicians as soon as possible.

Clinical Laboratory Findings

Creatinine

In hypertensive patients, greater than 50% increases in creatinine occurred in 0.4% of patients receiving Exforge and 0.6% receiving placebo. 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-treated patients.

Serum Potassium

In hypertensive patients, greater than 20% increases in serum potassium were observed in 2.8% of Exforge-treated patients compared to 3.4% of placebo-treated 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.

Blood Urea Nitrogen (BUN)

In hypertensive patients, greater than 50% increases in BUN were observed in 5.5% of Exforge-treated patients compared to 4.7% of placebo-treated patients. In heart failure patients, greater than 50% increases in BUN were observed in 16.6% of valsartan-treated patients compared to 6.3% of placebo-treated patients.

Drug Interactions

No drug interaction studies have been conducted with Exforge and other drugs, although studies have been conducted with the individual amlodipine and valsartan components, as described below:

Studies with 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.

Maalox® (antacid): Co-administration of the antacid Maalox with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil: A single 100 mg dose of sildenafil (Viagra®) 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.

Studies with 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.

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

CYP 450 Interactions

The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes. The inhibitory or induction potential of valsartan on CYP 450 is also unknown.

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.

Drug/Food Interactions

Studies with amlodipine: The bioavailability of amlodipine is not altered by the presence of food.

Studies with valsartan: Food decreases the exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%.

Carcinogenesis/Mutagenesis/Impairment of Fertility

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/m^2 basis, similar to the maximum recommended human dose [MRHD] of 10 mg amlodipine/day. For the rat, the highest dose was, on a mg/m^2 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/m^2 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/m^2 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/m^2 basis.

Pregnancy

Pregnancy Category C (first trimester) and D (second and third trimesters)

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

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/m^2 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. Amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 amlodipine besylate 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).

Labor and Delivery

The effect of Exforge on labor and delivery has not been studied.

Nursing Mothers

It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while amlodipine is administered.

It is not known whether valsartan is excreted in human milk, but valsartan was excreted in the milk of lactating rats. 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.

Pediatric Use

Safety and effectiveness of Exforge in pediatric patients have not been established.

Geriatric Use

In controlled clinical trials, 323 hypertensive patients treated with Exforge were ≥ 65 years and 79 were ≥ 75 years. No overall differences in the efficacy or safety of Exforge was observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Exforge

Exforge[®] (amlodipine and valsartan) has been evaluated for safety in over 2600 patients with hypertension; over 1440 of these patients were treated for at least 6 months and over 540 of these patients were treated for at least one year. Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy.

The overall frequency of adverse experiences was neither dose-related nor related to gender, age, or race. In placebo-controlled clinical trials, discontinuation due to side effects occurred in 1.8% of patients in the Exforge-treated patients and 2.1% in the placebo-treated group. The most common reasons for discontinuation of therapy with Exforge were peripheral edema (0.4%), and vertigo (0.2%).

The adverse experiences that occurred in placebo-controlled clinical trials in at least 2% of patients treated with Exforge but at a higher incidence in amlodipine/valsartan patients (n=1437) than placebo (n=337) included peripheral edema (5.4% vs. 3.0%), nasopharyngitis (4.3% vs. 1.8%), upper respiratory tract infection (2.9% vs 2.1%) and dizziness (2.1% vs 0.9%).

Orthostatic events (orthostatic hypotension and postural dizziness) were seen in less than 1% of patients.

Other adverse experiences that occurred in placebo-controlled clinical trials with Exforge ($\geq 0.2\%$) are listed below. It cannot be determined whether these events were causally related to Exforge.

Blood and Lymphatic System Disorders: Lymphadenopathy

Cardiac Disorders: Palpitations, tachycardia

Ear and Labyrinth Disorders: Ear pain

Gastrointestinal Disorders: Diarrhea, nausea, constipation, dyspepsia, abdominal pain, abdominal pain upper, gastritis, vomiting, abdominal discomfort, hemorrhoids, abdominal distention, dry mouth, flatulence, toothache, colitis

General Disorders and Administration Site Conditions: Fatigue, chest pain, asthenia, pitting edema, pyrexia, edema, pain,

Immune System Disorders: seasonal allergies

Infections and Infestations: Nasopharyngitis, sinusitis, influenza, bronchitis, pharyngitis, urinary tract infection, gastroenteritis, pharyngotonsillitis, bronchitis acute, viral infection, tonsillitis, tooth abscess, cystitis, pneumonia

Injury, Poisoning and Procedural Complications: Contusion, epicondylitis, joint sprain, limb injury, post procedural pain

Investigations: Cardiac murmur

Metabolism and Nutrition Disorders: Gout, non-insulin dependent diabetes mellitus, hypercholesterolemia

Musculoskeletal and Connective Tissue Disorders: Arthralgia, back pain, muscle spasms, pain in extremity, myalgia, osteoarthritis, joint swelling, musculoskeletal chest pain

Nervous System Disorders: Headache, sciatica, parasthesia, cervicobrachial syndrome, carpal tunnel syndrome, hypoaesthesia, sinus headache, somnolence

Psychiatric Disorders: Insomnia, anxiety, depression

Renal and Urinary Disorders: Hematuria, nephrolithiasis, pollakiuria

Reproductive System and Breast Disorders: Erectile dysfunction

Respiratory, Thoracic and Mediastinal Disorders: Cough, pharyngolaryngeal pain, sinus congestion, dyspnea, epistaxis, productive cough, dysphonia, nasal congestion,

Skin and Subcutaneous Tissue Disorders: Pruritus, rash, hyperhidrosis, eczema, erythema

Vascular Disorders: Flushing, hot flush

Isolated cases of the following clinically notable adverse events were also observed in clinical trials: exanthema, syncope, visual disturbance, hypersensitivity, tinnitus, and hypotension.

Amlodipine

Norvasc[®] has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. Other adverse events that have been reported <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, weight loss

Musculoskeletal System: arthrosis, muscle cramps

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

Respiratory System: dyspnea

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 events 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 the prescribing information for Norvasc.

Post-Marketing Experience

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

Diovan[®] 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 events, not listed above, occurring in $>0.2\%$ of patients in controlled clinical trials with valsartan are:

Body as a Whole: allergic reaction, asthenia

Musculoskeletal: muscle cramps

Neurologic and Psychiatric: paresthesia

Respiratory: sinusitis, pharyngitis

Urogenital: Impotence

Other reported events seen less frequently in clinical trials were: angioedema.

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

Post-Marketing Experience

The following additional adverse events have been reported in post-marketing experience with valsartan:

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

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

OVERDOSAGE

Information on 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 was 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.

Information on Valsartan

Limited data are available related to overdosage in humans. The most likely effect of overdose with valsartan would be peripheral vasodilation, hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. Depressed level of

consciousness, circulatory collapse and shock have been reported. If symptomatic hypotension should occur, supportive treatment should be instituted.

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 the salivation and diarrhea in the rat and vomiting in the marmoset at the highest dose (60 and 37 times, respectively, the maximum recommended human dose on a mg/m² basis). (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

DOSAGE AND ADMINISTRATION

Amlodipine is an effective treatment of hypertension in once daily doses of 2.5 mg-10 mg while valsartan is effective in doses of 80 mg-320 mg. In clinical trials with Exforge[®] (amlodipine and valsartan) using amlodipine doses of 5 mg-10 mg and valsartan doses of 160 mg-320 mg, the antihypertensive effects increased with increasing doses.

The hazards (see WARNINGS) of valsartan are generally independent of dose; those of amlodipine are a mixture of dose-dependent phenomena (primarily peripheral edema) and dose-independent phenomena, the former much more common than the latter. Therapy with any combination of amlodipine and valsartan will thus be associated with both sets of dose-independent hazards.

A patient who experiences dose-limiting adverse reactions on either component alone may be switched to Exforge containing a lower dose of that component in combination with the other to achieve similar blood pressure reductions. The clinical response to Exforge should be subsequently evaluated and if blood pressure remains uncontrolled after 3-4 weeks of therapy, the dose may be titrated up to a maximum of 10/320 mg.

To minimize dose-independent hazards, it is usually appropriate to begin therapy with EXFORGE only after a patient has failed to achieve the desired antihypertensive effect with one or the other monotherapy.

Dose Titration Guided by Clinical Effect

A patient whose blood pressure is not adequately controlled with amlodipine (or another DHP CCB) alone or with valsartan (or another ARB) alone may be switched to combination therapy with Exforge.

Replacement Therapy

For convenience, patients receiving amlodipine and valsartan from separate tablets may instead wish to receive tablets of Exforge containing the same component doses.

HOW SUPPLIED

Exforge[®] (amlodipine and valsartan) is available as tablets containing amlodipine besylate equivalent to 5 mg, or 10 mg of amlodipine free-base with valsartan 160 mg or 320 mg, providing for the following available combinations: 5/160 mg, 10/160 mg, 5/320 mg and 10/320 mg.

All strengths are packaged in bottles of 30 and 90 count, and unit dose blister packages.

5/160 mg Tablets - dark yellow, ovaloid shaped, film coated tablet with beveled edge, debossed with “NVR” on one side and “ECE” on the other side.

Bottles of 30 NDC # 0078-0488-15

Bottles of 90 NDC # 0078-0488-34

Unit Dose 100 tablets (10 X 10 tablets blister cards) NDC # 0078-0488-35

10/160 mg Tablets - light yellow, ovaloid shaped, film coated tablet with beveled edge, debossed with “NVR” on one side and “UIC” on the other side.

Bottles of 30 NDC # 0078-0489-15

Bottles of 90 NDC # 0078-0489-34

Unit Dose 100 tablets (10 X 10 tablets blister cards) NDC # 0078-0489-35

5/320 mg Tablets - very dark yellow, ovaloid shaped, film coated tablet with beveled edge, debossed with “NVR” on one side and “CSF” on the other side.

Bottles of 30 NDC # 0078-0490-15

Bottles of 90 NDC # 0078-0490-34

Unit Dose 100 tablets (10 X 10 tablets blister cards) NDC # 0078-0490-35

10/320 mg Tablets - dark yellow, ovaloid shaped, film coated tablet with beveled edge, debossed with “NVR” on one side and “LUF” on the other side.

Bottles of 30 NDC # 0078-0491-15

Bottles of 90 NDC # 0078-0491-34

Unit Dose 100 tablets (10 X 10 tablets blister cards) NDC # 0078-0491-35

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.] Protect from moisture.

*Viagra[®] is a registered trademark of Pfizer, Inc.

**Norvasc[®] is a registered trademark of Pfizer, Inc.

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Patient Information

EXFORGE[®], (X-PHORJ)

(amlodipine and valsartan) Tablets
5/160 mg, 10/160 mg, 5/320 mg, 10/320 mg

Read the Patient Information that comes with EXFORGE 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?

Taking EXFORGE during pregnancy can cause injury and even death to your unborn baby. If you get pregnant, stop taking EXFORGE and call your doctor right away. Talk to your doctor about other ways to lower your blood pressure if you plan to become pregnant.

What is EXFORGE?

EXFORGE is a prescription medicine used to treat high blood pressure (hypertension). EXFORGE contains two prescription medicines that work together to lower blood pressure: amlodipine, a calcium channel blocker, and valsartan, an angiotensin receptor blocker. EXFORGE should not be used before other medicines have been tried first to treat high blood pressure.

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 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.

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

Who should NOT take EXFORGE?

Do not take EXFORGE if you are allergic to any of the ingredients in EXFORGE. See the end of this leaflet for a complete list of ingredients in EXFORGE.

What should I tell my doctor before taking EXFORGE?

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

- have heart problems
- have liver problems
- have kidney problems
- are vomiting or having a lot of diarrhea
- **are pregnant or plan to become pregnant.** See “What is the most important information I should know about EXFORGE?”
- **are breastfeeding or plan to breastfeed.** EXFORGE may pass into your milk. Do not breastfeed while you are taking EXFORGE.

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 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 (also called “diuretics”)
- potassium supplements
- a salt substitute

If you take a beta blocker medicine and your doctor tells you to stop taking it while you are taking EXFORGE, follow your doctor’s instructions very carefully to slowly and safely stop the beta blocker medicine. Stopping beta blocker medicines too quickly can cause chest pain (angina), heart attack, abnormal heart rhythm or high blood pressure. Taking EXFORGE does **not** help to prevent these effects. If you do not know if you take a beta blocker medicine, contact your doctor or pharmacist.

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 do I take EXFORGE?

- Take EXFORGE exactly as your doctor tells you.
- Take Exforge at the same time each day.
- 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, call your doctor or Poison Control Center, or go to the emergency room.
- Tell all your doctors or dentist you are taking EXFORGE if you:
 - are going to have surgery
 - go for kidney dialysis

What are the possible side effects of EXFORGE?

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

- **injury or death of unborn babies.** See “**What is the most important information I should know about EXFORGE?**”
- **low blood pressure** (hypotension). Low blood pressure is most likely to happen if you also take water pills, are on a low salt diet, have heart problems, or get sick with vomiting or diarrhea. Lie down if you feel faint or dizzy. Call your doctor right away.
- **more chest pain (angina) and heart attacks** in people that already have severe heart problems. This may happen when you start EXFORGE or when there is an increase in your dose of EXFORGE. Get emergency help if you get worse chest pain or chest pain that does not go away.
- **kidney problems.** Kidney problems may get worse in people that already have kidney disease. Some people will have changes in blood tests for kidney function and need a lower dose of EXFORGE. Call your doctor if you get swelling in your feet, ankles, or hands or unexplained weight gain.

- **laboratory blood test changes in patients with congestive heart failure.** In studies with valsartan, some patients with congestive heart failure had blood tests that showed increased potassium and decrease in kidney function.
- **allergic reactions**

The **most common** side effects that occur more frequently with Exforge than placebo (sugar pill) are:

- swelling (edema) of the hands, ankles, or feet.
- nasal congestion, sore throat and discomfort when swallowing
- upper respiratory tract infection (head or chest cold)
- dizziness

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. For more information, ask your doctor or pharmacist.

How should I store EXFORGE?

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

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

General Information about EXFORGE

Medicines are sometimes prescribed for conditions that are not mentioned in the patient information leaflet. Do not use EXFORGE for a condition for which it was not prescribed. Do not give EXFORGE 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. If you would like more information about EXFORGE, talk with your doctor. You can ask your doctor or pharmacist for information about EXFORGE that is written for health professionals. For more information go to www.EXFORGE.com or call 1-888-8-EXFORGE (1-888-839-3674).

What are the ingredients in EXFORGE?

Active ingredients: amlodipine besylate and valsartan

The inactive ingredients of all strengths of the tablets are colloidal silicon dioxide, crospovidone, magnesium stearate and microcrystalline cellulose. Additionally, the 5/320 mg and 10/320 mg strengths contain iron oxide yellow and sodium starch glycolate. The film coating contains hypromellose, iron oxides, polyethylene glycol, talc and titanium dioxide.

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