For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

TRIVALZAAR

(Valsartan, Amlodipine and Hydrochlorothiazide Tablets)

COMPOSITION:

TRIVALZAAR 80

Each film coated tablet contains:
Valsartan I.P. 80 mg
Amlodipine Besilate I. P. Equivalent to Amlodipine 5 mg
Hydrochlorothiazide I. P. 12.5 mg
Color: Titanium Dioxide I.P.

TRIVALZAAR 160

Each film coated tablet contains:
Valsartan I.P. 160 mg
Amlodipine Besilate I.P. Equivalent to Amlodipine 5 mg
Hydrochlorothiazide I. P. 12.5 mg
Color: Titanium Dioxide I.P.

WARNING: FETAL TOXICITY

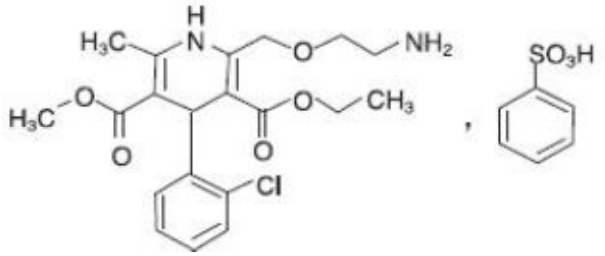
When pregnancy is detected, discontinue product as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

DESCRIPTION

TRIVALZAAR is a fixed dose combination of Valsartan, Amlodipine and Hydrochlorothiazide.

Amlodipine

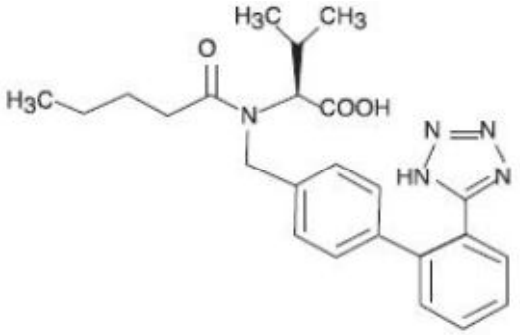
Amlodipine is a white or almost white powder, freely soluble in methanol; sparingly soluble in ethanol (95 per cent); slightly soluble in 2-propanol and in name is 3-ethyl5-methyl (4RS)-2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5 dicarboxylate benzene sulphonate and Its empirical formula is $C_{26}H_{31}ClN_2O_8S$ and its molecular weight is 567.1 and its structural formula is:



Valsartan

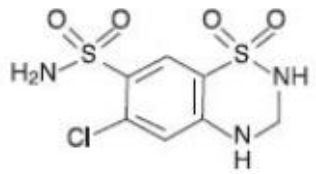
Valsartan is a nonpeptide, orally active, and specific angiotensin II antagonist acting on the AT_1

receptor subtype. Valsartan is a white to almost white powder, Very soluble in methanol; practically insoluble in water, Valsartan's chemical name is -pentanonyl-N- -(1H-tetrazol-5-yl) biphenyl-4-ylmethyl]-L-valine and its empirical formula is $C_{24}H_{29}N_5O_3$ and its molecular weight is 435.5 and its structural formula is:



Hydrochlorothiazide

Hydrochlorothiazide is a White or almost white, crystalline powder; odourless. Soluble in acetone; sparingly soluble in ethanol (95%); very slightly soluble in water. It dissolves in dilute solutions of alkali hydroxides. Hydrochlorothiazide is chemically described as 6-chloro-3, 4-dihydro-2H-1, 2, 4-benzothiadiazine-7-sulphonamide1, 1-dioxide. Hydrochlorothiazide is a thiazide diuretic. Its empirical formula is $C_7H_8ClN_3O_4S_2$, its molecular weight is 297.7, and its structural formula is:



PHARMACODYNAMIC

Mechanism of action

The active ingredients of FDC 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 (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect. Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

Valsartan

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme(ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, witheffects 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 AT1 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 rennin 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, increase 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.

PHARMACOKINETIC

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 coadministered drugs are unlikely because of the low extent of metabolism. Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance).

Hydrochlorothiazide

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.

INDICATIONS

FDC of Valsartan, Amlodipine and hydrochlorothiazide is indicated for the treatment of essential hypertension. This fixed combination drug is not indicated for the initial therapy of hypertension.

DOSAGE AND ADMINISTRATION

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 FDC of Valsartan, Amlodipine and Hydrochlorothiazide. The maximum recommended dose of FDC of Valsartan, Amlodipine and Hydrochlorothiazide is 10/320/25 mg. FDC of Valsartan, Amlodipine and Hydrochlorothiazide may be administered with or without food. No initial dosage adjustment is required for elderly patients.

Renal impairment: The usual regimens of therapy with FDC of Valsartan, Amlodipine and patients with more severe renal impairment, loop diuretics are preferred to thiazides, so avoid use of FDC of Valsartan, Amlodipine and Hydrochlorothiazide.

Hepatic impairment: Avoid FDC of Valsartan, Amlodipine and Hydrochlorothiazide 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.

Add-on / Switch Therapy
FDC of Valsartan, Amlodipine and Hydrochlorothiazide 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 FDC of Valsartan, Amlodipine and Hydrochlorothiazide may be switched to FDC of Valsartan, Amlodipine and Hydrochlorothiazide containing a lower dose of that component to achieve similar blood pressure reductions.

Replacement Therapy
FDC of Valsartan, Amlodipine and Hydrochlorothiazide may be substituted for the individually titrated components.

CONTRAINDICATIONS
Because of the hydrochlorothiazide component, this FDC is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs. Hypersensitivity to any of the active ingrediants, or to any of the excipients.

WARNINGS AND PRECAUTIONS
Fetal/Neonatal Morbidity and Mortality FDC of Valsartan, Amlodipine and Hydrochlorothiazide 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.

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Diovan as soon as possible.

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 FDC of Valsartan, Amlodipine and Hydrochlorothiazide (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 FDC of Valsartan, Amlodipine and Hydrochlorothiazide. FDC of Valsartan, Amlodipine and Hydrochlorothiazide 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 FDC of Valsartan, Amlodipine and Hydrochlorothiazide in patients with aortic or mitral stenosis or obstructive hypertrophic cardiomyopathy. If excessive hypotension occurs with FDC of Valsartan, Amlodipine and Hydrochlorothiazide, 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 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.

Impaired Hepatic Function
Amlodipine is extensively metabolized by the liver and the plasma elimination half-life (t½) 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 FDC of Valsartan, Amlodipine and Hydrochlorothiazide in patients with severe hepatic impairment. When administering FDC of Valsartan, Amlodipine and Hydrochlorothiazide 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.

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 FDC of Valsartan, Amlodipine and Hydrochlorothiazide in severe renal disease (creatinine clearance 30 mL/min). The usual regimens of therapy with FDC of Valsartan, Amlodipine and Hydrochlorothiazide There is no experience in the use of FDC of Valsartan, Amlodipine and Hydrochlorothiazide in patients with a recent kidney transplant.

Heart Failure
FDC of Valsartan, Amlodipine and Hydrochlorothiazide 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.

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.

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

Lithium Interaction
Lithium generally should not be given with thiazides.

Electrolytes and Metabolic Imbalances
Amlodipine -Valsartan - Hydrochlorothiazide
In the controlled trial of FDC of Valsartan, Amlodipine and Hydrochlorothiazide 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 FDC of Valsartan, Amlodipine and Hydrochlorothiazide (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). The incidence of hyperkalemia (serum potassium >5.7 mEq/L) was 0.4% with FDC of Valsartan, Amlodipine and Hydrochlorothiazide compared to 0.2-0.7% with the dual therapies. Monitor serum electrolytes periodically based on FDC of Valsartan, Amlodipine and Hydrochlorothiazide

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 FDC of Valsartan, Amlodipine and Hydrochlorothiazide 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. FDC of Valsartan, Amlodipine and Hydrochlorothiazide 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.

Acute Myopia and Secondary Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decrease

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

DRUG INTERACTIONS

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 (valsartan) was coadministered with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. The valsartanatenolol combination was more antihypertensive than either component, but it did not lower the heart rate more than atenolol alone. Coadministration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.

CYP 450 Interactions: In vitro metabolism studies indicate that CYP 450 mediated drug interactions between valsartan and coadministered drugs are unlikely because of the low extent of metabolism.

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

Potassium: Concomitant use of valsartan with other agents that block the renin-angiotensin system, 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. If co-medication is considered necessary, monitoring of serum potassium is advisable.

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

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

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

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

Lithium: Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists, including valsartan. Monitor serum lithium levels during concomitant use.

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 increase 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 FDC of Valsartan, Amlodipine and Hydrochlorothiazide.
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.
Clinical Laboratory Test Findings
Creatinine: In hypertensive patients, greater than 50% increases in creatinine reported in 2.1% of FDC of Valsartan, Amlodipine and Hydrochlorothiazide 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 reported 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 FDC of Valsartan, Amlodipine and Hydrochlorothiazide treated patients.

Blood Urea Nitrogen (BUN): In hypertensive patients, greater than 50% increases in BUN were observed in 30% of FDC of Valsartan, Amlodipine and Hydrochlorothiazide-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 FDC of Valsartan, Amlodipine and Hydrochlorothiazide-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 FDC of Valsartan, Amlodipine and Hydrochlorothiazide- 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.

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

USE IN SPECIFIC POPULATION
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 FDC of Valsartan, Amlodipine and Hydrochlorothiazide 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 FDC of Valsartan, Amlodipine and Hydrochlorothiazide, the physician should discontinue FDC of Valsartan, Amlodipine and Hydrochlorothiazide treatment as soon as possible. The physician should inform the patien about potential risks to the fetus based on the time of gestational exposure to FDC of Valsartan, Amlodipine and Hydrochlorothiazide (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 FDC of Valsartan, Amlodipine and Hydrochlorothiazide 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 FDC of Valsartan, Amlodipine and Hydrochlorothiazide 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.

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.

Pediatric Use
The safety and effectiveness of FDC of Valsartan, Amlodipine and Hydrochlorothiazide in pediatric patients have not been established.

Geriatric Use
No overall differences in the efficacy or safety of FDC of Valsartan, Amlodipine and Hydrochlorothiazide were observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS
The most frequent adverse events that reported in the active controlled clinical trial in at least 2% of patients treated with FDC of Valsartan, Amlodipine and Hydrochlorothiazide are Dizziness, Edema, Headache, Dyspepsia, Fatigue, Muscle spasms, Back pain, Nausea, Nasopharyngitis. Orthostatic events (orthostatic hypotension and postural dizziness) were reported in 0.5% of patients.
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
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: micturition frequency, micturition disorder, nocturia
Autonomic Nervous System: sweating increased
Metabolic and Nutritional: hyperglycemia, thirst
Hemopoietic: leukopenia, purpura, thrombocytopenia
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.

The following additional adverse reactions have been reported in post-marketing experience with amlodipine: Gynecomastia, Jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis).

Valsartan
Clinical Studies Experience
Adult Hypertension
Valsartan (valsartan) has been evaluated for safety in more than 4,000 patients, including over 400 treated for over 6 months, and more than 160 for over 1 year. Adverse reactions have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The overall incidence of adverse reactions with Valsartan was similar to placebo. The overall frequency of adverse reactions was neither dose-related nor related to gender, age, race, or regimen. Discontinuation of therapy due to side effects was required in 2.3% of valsartan patients and 2.0% of placebo patients. The most common reasons for discontinuation of therapy with Valsartan were headache and dizziness.

The adverse reactions that occurred in placebo-controlled clinical trials in at least 1% of patients treated with Valsartan and at a higher incidence in valsartan (n=2,316) than placebo (n=888) patients included viral infection (3% vs. 2%), fatigue (2% vs. 1%), and abdominal pain (2% vs. 1%).

Headache, dizziness, upper respiratory infection, cough, diarrhea, rhinitis, sinusitis, nausea, pharyngitis, edema, and arthralgia occurred at a more than 1% rate but at about the same incidence in placebo and valsartan patients.

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 ($p < 0.001$).

Dose-related orthostatic effects were seen in less than 1% of patients. An increase in the incidence of dizziness was observed in patients treated with Valsartan 320 mg (8%) compared to 10 to 160 mg (2% to 4%).

Valsartan has been used concomitantly with hydrochlorothiazide without evidence of clinically important adverse interactions.
Other adverse reactions that occurred in controlled clinical trials of patients treated with Valsartan (>0.2% of valsartan patients) are listed below. It cannot be determined whether these events were causally related to Valsartan.
Body as a Whole: Allergic reaction and asthenia
Cardiovascular: Palpitations
Dermatologic: Pruritus and rash
Digestive: Constipation, dry mouth, dyspepsia, and flatulence
Musculoskeletal: Back pain, muscle cramps, and myalgia
Neurologic and Psychiatric: Anxiety, insomnia, paresthesia, and somnolence
Respiratory: Dyspnea
Special Senses: Vertigo
Urogenital: Impotence
Other reported events seen less frequently in clinical trials included chest pain, syncope, anorexia, vomiting, and angioedema.

Pediatric Hypertension
Valsartan has been evaluated for safety in over 400 pediatric patients aged 6 to 17 years and more than 160 pediatric patients aged 6 months to 5 years. No relevant differences were identified between the adverse experience profile for pediatric patients aged 6-16 years and that previously reported for adult patients. Headache and hyperkalemia were the most common adverse events suspected to be study drug-related in older children (6 to 17 years old) and younger children (6 months to 5 years old), respectively. Hyperkalemia was mainly observed in children with underlying renal disease. Neurocognitive and developmental assessment of pediatric patients aged 6 to 16 years revealed no overall clinically relevant adverse impact after treatment with Valsartan for up to 1 year. Valsartan is not recommended for pediatric patients under 6 years of age. In a study (n=90) of pediatric patients (1-5 years), two deaths and three cases of on-treatment transaminase elevations were seen in the one-year open-label extension phase. These 5 events occurred in a study population in which patients frequently had significant co-morbidities. A causal relationship to Valsartan has not been established. In a second study in

which 75 children aged 1 to 6 years were randomized, no deaths and one case of marked liver transaminase elevations occurred during a 1 year open-label extension.

Heart Failure

The adverse experience profile of Valsartan in heart failure patients was consistent with the pharmacology of the drug and the health status of the patients. In the Valsartan Heart Failure Trial, comparing valsartan in total daily doses up to 320 mg (n=2,506) to placebo (n=2,494), 10% of valsartan patients discontinued for adverse reactions vs. 7% of placebo patients. The table shows adverse reactions in double-blind short-term heart failure trials, including the first 4 months of the Valsartan Heart Failure Trial, with an incidence of at least 2% that were more frequent in valsartan-treated patients than in placebo-treated patients. All patients received standard drug therapy for heart failure, frequently as multiple medications, which could include diuretics, digitalis, and beta-blockers. About 93% of patients received concomitant ACE inhibitors.

	Valsartan (n=3,282)	Placebo (n=2,740)
Dizziness	17%	9%
Hypotension	7%	2%
Diarrhea	5%	4%
Arthralgia	3%	2%
Fatigue	3%	2%
Back Pain	3%	2%
Dizziness, postural	2%	1%
Hyperkalemia	2%	1%
Hypotension, postural	2%	1%

Discontinuations occurred in 0.5% of valsartan-treated patients and 0.1% of placebo patients for each of the following: elevations in creatinine and elevations in potassium. Other adverse reactions with an incidence greater than 1% and greater than placebo included headache NOS, nausea, renal impairment NOS, syncope, blurred vision, upper abdominal pain and vertigo. (NOS = not otherwise specified). From the long-term data in the Valsartan Heart Failure Trial, there did not appear to be any significant adverse reactions not previously identified.

Post-Myocardial Infarction

The safety profile of Valsartan was consistent with the pharmacology of the drug and the background diseases, cardiovascular risk factors, and clinical course of patients treated in the post-myocardial infarction setting. The table shows the percent of patients discontinued in the valsartan and captopril-treated groups in the Valsartan in Acute Myocardial Infarction Trial (VALIANT) with a rate of at least 0.5% in either of the treatment groups. Discontinuations due to renal dysfunction occurred in 1.1% of valsartan-treated patients and 0.8% of captopril-treated patients.

	Valsartan (n=4,885)	Captopril (n=4,879)
Discontinuation for adverse reaction	5.8%	7.7%
Adverse reactions		
Hypotension NOS	1.4%	0.8%

Cough	0.6%	2.5%
Blood creatinine increased	0.6%	0.4%
Rash NOS	0.2%	0.6%

Post-Marketing Experience
The following additional adverse reactions have been reported in post-marketing experience:
Hypersensitivity: There are rare reports of angioedema. Some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Valsartan should not be readministered to patients who have had angioedema.
Digestive: Elevated liver enzymes and very rare reports of hepatitis
Renal: Impaired renal function, renal failure
Clinical Laboratory Tests: Hyperkalemia
Dermatologic: Alopecia
Blood and Lymphatic: There are very rare reports of thrombocytopenia Vascular: Vasculitis Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

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

Hydrochlorothiazide
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 angiitis (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.

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/m^2 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 and Hydrochlorothiazide
In rats and marmosets, single oral doses of valsartan up to 1524 and 762 mg/kg in combination with hydrochlorothiazide at doses up to 476 and 238 mg/kg, respectively, were very well tolerated without any treatment-related effects. These no adverse effect doses in rats and marmosets, respectively, represent 46.5 and 23 times the maximum recommended human dose (MRHD) of valsartan and 188 and 113 times the MRHD of hydrochlorothiazide on a mg/m^2 basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient.)

EXPIRY DATE
Do not use later than expiry date.

STORAGE
Store at a temperature not exceeding 30^oC, protected from light and moisture.
Keep out of reach of children.

PRESENTATION
Trivalzaar 80 and Trivalzaar 160 are available in strip pack of 10 tablets.

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