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

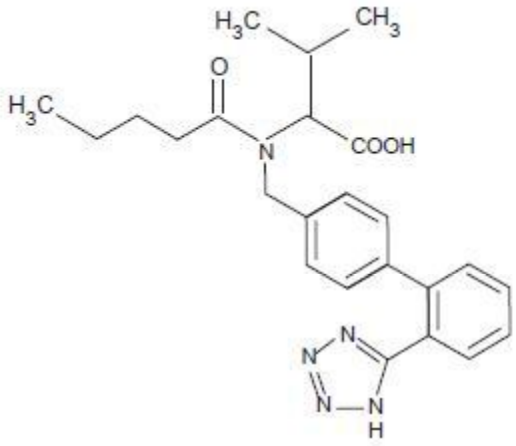
VALZAAR SM
(Valsartan and S-Amlodipine Besylate Capsules)

COMPOSITION
Each hard gelatin capsule contains:
Valsartan I.P. 80 mg
S-Amlodipine Besylate I.P. equivalent to S-Amlodipine 2.5 mg
Approved colours used in hard gelatin capsule shells

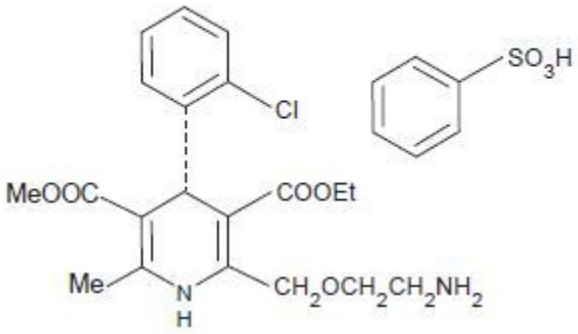
DESCRIPTION
Valsartan
Valsartan is a nonpeptide, orally active, and specific angiotensin II antagonist acting on the AT1 receptor subtype. Valsartan is chemically described as N-(1- oxopentyl)-N-[[2-(1H-tetrazol-5-yl) [1, 1-biphenyl]-4-yl] methyl]-L-valine. Its empirical formula is $C_{24}H_{29}N_5O_3$ and its molecular weight is 435.52.

Amlodipine
S-Amlodipine Besylate is a white to pale yellow powder. It is soluble in methanol. It is chemically described as (S)-3-ethyl-5-methyl-2-(2- aminoethoxymethyl) -4- (2-chlorophenyl) 1, 4-dihydro-6-methyl -3, 5- pyridinedicarboxylate benzenesulphonate. Its empirical formula is $C_{20}H_{25}ClN_2O_5$. $C_6H_6O_3S$ with a molecular weight of 567.1.

The structural formula of Valsartan and S-Amlodipine Besylate are as follows:



Valsartan



S-Amlodipine Besylate

PHARMACOLOGICAL PROPERTIES
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.

MECHANISM OF ACTION

Valsartan

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin - converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT 1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis. Valsartan has much greater affinity (about 20,000-fold) for the AT 1 receptor than for the AT 2 receptor.

S-Amlodipine

S-Amlodipine, an isomer of amlodipine belongs to the dihydropyridine class of calcium channel blockers. S-Amlodipine exerts its antihypertensive effect by inhibiting calcium influx into cardiac and vascular smooth muscle via L-type calcium channels.

PHARMACODYNAMICS

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. 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 multipledose 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. In multiple-dose studies in hypertensive patients, Valsartan had no notable effects on total cholesterol, fasting triglycerides, fasting serum glucose, or uric acid. Administration of Valsartan to patients with essential hypertension results in a significant reduction of sitting, supine, and standing systolic and diastolic blood pressure, usually with little or no orthostatic change.

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs at approximately 2 hours, and maximum reduction of blood pressure is achieved within 6 hours. The antihypertensive effect persists for 24 hours after dosing, but there is a decrease from peak effect at lower doses (40 mg) presumably reflecting loss of inhibition of angiotensin II. In long-term follow-up studies (without placebo control), the effect of Valsartan appeared to be maintained for up to two years. The antihypertensive effect is independent of age, gender or race. Abrupt withdrawal of Valsartan has not been associated with a rapid increase in blood pressure. In controlled trials, the antihypertensive effect of once-daily Valsartan 80 mg was similar to that of once-daily enalapril 20 mg or once-daily lisinopril 10 mg. There was essentially no change in heart rate in Valsartantreated patients in controlled trials.

S-Amlodipine

S-Amlodipine is a long-acting calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. The contractile process of cardiac muscle and vascular smooth muscle are dependent upon movement of extra cellular calcium ions into these cells through specific ion channels. By inhibiting calcium ion influx this product directly diastoles vascular smooth muscle, resisting hypertension.

PHARMACOKINETICS

Valsartan

Absorption

Valsartan peak plasma concentration is reached 2 to 4 hours after dosing. Valsartan shows biexponential decay kinetics following intravenous administration, with an average elimination half-life of about 6 hours. Absolute bioavailability for Valsartan 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%. AUC and C_{max} values of Valsartan increase approximately linearly with increasing dose over the clinical dosing range. Valsartan does not accumulate appreciably in plasma following repeated administration.

Metabolism and Elimination

Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). 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 isozymes.

Distribution

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

Special Populations

Pediatric:

The pharmacokinetics of Valsartan have not been investigated in patients < 18 years of age.

Geriatric:

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:

Pharmacokinetics of Valsartan does not differ significantly between males and females.

Heart Failure:

The average time to peak concentration and elimination half-life of Valsartan in heart failure patients are similar to that observed in healthy volunteers. Age does not affect the apparent clearance in heart failure patients.

Renal Insufficiency:
There is no apparent correlation between renal functions (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-tomoderate 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:
On average, patients with mild-to-moderate chronic liver disease have twice the exposure (measured by AUC values) to Valsartan of healthy volunteers. In general, no dosage adjustment is needed in patients with mild-to-moderate liver disease. Care should be exercised in patients with liver disease.

S-Amlodipine
Absorption
After oral administration of (S)-amlodipine besylate tablet, the blood-drug concentration reaches peak value within 6-12 hrs. The absolute bioavailability has been estimated to be in between 64-80% and the apparent distribution volume is approximately 21 L/kg.

Distribution
The blood-drug concentration comes up to homeostasis after successive administration with once a day for 7-8 days. Approximately 93% of the circulating drug is bound to plasma proteins.

Metabolism and Elimination
S-Amlodipine besylate is extensively converted to inactive metabolites via hepatic metabolism. S-Amlodipine is excreted out along with urine, with 10% of the parent, and 60% of the metabolites. The terminal elimination half-life for S-Amlodipine is 35-50 hrs. The average final elimination half-life period of (S)-amlodipine is 49.6 hrs while for (R)-amlodipine it is 34.9 hrs. After oral dosing with fixed dose combination of Valsartan-80mg and S-Amlodipine-2.5mg in healthy volunteers, maximum serum concentrations was found to be 7.78 ng/ml, T_{max} 3.52 hours and AUC 9.52 ng.h/ml for Valsartan and for S-Amlodipine maximum serum concentrations was found to be 0.22 ng/ml, T_{max} 7.70 hours and AUC 4.48 ng.h/ml.

INDICATIONS
Valzaar SM is indicated for the treatment of Hypertension.

DOSAGE AND ADMINISTRATION
The recommended dose of Valzaar SM is one capsule once a day.

CONTRAINDICATIONS
Valzaar SM is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS AND PRECAUTION

Valsartan

Pregnancy Category D

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 Valsartan as soon as possible.

Hypotension

Excessive hypotension was rarely seen (0.1%) in patients with uncomplicated hypertension treated with Valsartan alone. 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. This condition should be corrected prior to administration of Valsartan, or the treatment should start under close medical supervision. Caution should be observed when initiating therapy in patients with heart failure or post-myocardial infarction patients. 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 valsartantreated 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.

If excessive hypotension occurs, the patient should be placed in the 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.

Impaired Renal Function

Changes in renal function including acute renal failure can be caused by drugs that inhibit the renin-angiotensin system and by diuretics. Patients whose renal function may depend in part on the activity of the renin-angiotensin system (e.g. patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing acute renal failure on Valsartan. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on Valsartan.

Hyperkalemia

Some patients with heart failure have developed increases in potassium. 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 Valsartan may be required.

Amlodipine:

Hepatic failure patients: Similar to other calcium antagonist, the half life of S-Amlodipine is

prolonged in patients with impaired liver function. So, caution should be exercised in such patients. Renal failure patients: The normal dose may be adopted. This product is not dialyzed.

Use in Pregnancy, Nursing mothers and Children:
Pregnant Women & Nursing Mothers:
S-Amlodipine should be recommended only while there is no other safer alternative and the potential benefit outweighs the potential risk to the fetus. In the absence of this information, it is recommended that nursing should be discontinued while this product is administered.

Children:
Safety and effectiveness of S Amlodipine in children have not been established.

DRUG INTERACTIONS
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 Olmesartan 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.

S-Amlodipine
S-Amlodipine has been safely administered with thiazide diuretics, beta adrenoceptor blocking drugs, angiotensin converting enzyme inhibitors, long acting nitrates, sublingual glyceryl trinitrate, nonsteroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic agents. Co administration of S-Amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers. Co administration of cimetidine did not alter the pharmacokinetics of S-amlodipine.

In healthy volunteers, co administration of S-Amlodipine did not significantly alter the effect of warfarin on prothrombin time. The introduction of S-Amlodipine is not likely to result in the need for modification of an established warfarin regimen.

ADVERSE REACTIONS

Valsartan
Adverse experiences with Valsartan were generally mild and transient in nature. The overall incidence of adverse experiences with Valsartan was similar to placebo. The most commonly reported adverse events with Valsartan in clinical trials were headache, dizziness, viral infection, fatigue, abdominal pain, upper respiratory tract infection, cough, diarrhoea, rhinitis, sinusitis, nausea, pharyngitis, edema, arthralgia.

Clinical Laboratory Test Findings
Creatinine:
Minor elevations in creatinine occurred in 0.8% of patients taking Valsartan and 0.6% given placebo in controlled clinical trials of hypertensive patients.

Hemoglobin and Hematocrit:
Greater than 20% decreases in hemoglobin and hematocrit were observed in 0.4% and 0.8%, respectively, of Valsartan patients, compared with 0.1% and 0.1% in placebo-treated patients.

One Valsartan patient discontinued treatment for microcytic anemia.

Liver function tests:
Occasional elevations (greater than 150%) of liver chemistries occurred in Valsartan-treated patients. Three patients (< 0.1%) treated with Valsartan-discontinued treatment for elevated liver chemistries.

Neutropenia:
Neutropenia was observed in 1.9% of patients treated with Valsartan and 0.8% of patients treated with placebo.

Serum Potassium:
In hypertensive patients, greater than 20% increases in serum potassium were observed in 4.4% of Valsartan-treated patients compared to 2.9% of placebo-treated patients.

S-Amlodipine
S-Amlodipine is generally well tolerated. The most commonly observed side effects are headache, edema, fatigue, flushing and dizziness. Less common side effects include nausea, abdominal pain, somnolence and palpitations. Rare side effects include muscle cramps, frequency of micturition or nocturia, coughing, breathlessness, epistaxis, impotence, nervousness and conjunctivitis. No clinically significant pattern of laboratory test abnormalities related to S-Amlodipine has been observed.

S-Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids. S-Amlodipine has been used safely in patients with well-compensated congestive heart failure, peripheral vascular disease, chronic obstructive pulmonary disease, abnormal lipid profiles and diabetes mellitus. Like other calcium antagonist, adverse reaction seldom causes the adverse reaction of myocardial infarction and pectoralgia, which cannot be clearly distinguished from fundamental diseases of patients.

OVERDOSAGE

Valsartan
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. Valsartan is not removed from the plasma by hemodialysis.

S-Amlodipine
Available data suggests that the gross over dosage could result in excessive peripheral vasodilation with subsequent marked and probably prolonged hypotension. Since absorption of S-Amlodipine is slow, gastric lavage should be performed. Active cardiovascular support including monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output should be given. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. A vasoconstrictor agent may be helpful in restoring vascular tone and blood pressure provided that there is no contraindication to its use. Since S-Amlodipine is highly protein bound, dialysis is unlikely to be of benefit.

EXPIRY DATE
Do not use after the date of expiry.

STORAGE
Store in a dry place at a temperature not exceeding 30^{o}C, protected from light and moisture.
Keep all medicines out of reach of children.

PRESENTATION
Valzaar SM is available in strips of 10 capsules.

MARKETED BY

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IN/VALZAAR SM 2.5,80mg /SEPT-15/03/PI