AVSAR®
(Valsartan+AmlodipineUSP)

ایوسار

COMPOSITION

AVSAR 80/5 mg Tablet
Each film coated tablet contains:
Valsartan USP.....80mg
Amlodipine (as besylate) USP.....5mg
AVSAR 160/5 mg Tablet
Each film coated tablet contains:
Valsartan USP.....160mg
Amlodipine (as besylate) USP.....5mg
AVSAR 160/10 mg Tablet
Each film coated tablet contains:
Valsartan USP.....160mg
Amlodipine (as besylate) USP....10mg

(USP Specs.)

WARNING: PREGNANCY AND FETAL TOXICITY
Drugs that act directly on the renin-angiotensin system such as Valsartan can cause injury and death to the developing fetus when taken during pregnancy. When pregnancy is detected, Valsartan should be discontinued as soon as possible.

DESCRIPTION
Avsar is a combination product containing Valsartan and amlodipine with additive effects on blood pressure reduction than each agent alone.

Valsartan is a non-peptide, orally active, and specific angiotensin II receptor blocker acting on the AT1 receptor subtype used as an antihypertensive agent. Its chemical name is N-(1-oxopentyl)-N-[[2'-(1H-tetrazol-5-yl) [1, 1'-biphenyl]-4-yl] methyl]-L-valine. The molecular formula is $C_{24}H_{29}N_5O_3$

Amlodipine besylate is a dihydropyridine long-acting calcium channel blocker. Amlodipine besylate monohydrate is chemically described as 3-ethyl-5-methyl (±)-2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-1, 4-dihydro-6-methyl-3, 5-pyridinedicarboxylate, monobenzene sulphonate monohydrate. Its molecular formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S \cdot H_2O$

CLINICAL PHARMACOLOGY

Pharmacodynamics

Mechanism of Action
Avsar combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: amlodipine belongs to the calcium antagonist class and valsartan to the angiotensin II antagonist class of medicines. The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Amlodipine
Amlodipine is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Amlodipine binds to both dihydropyridine and non dihydropyridine 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.
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 thus contributing to the antihypertensive effects. Its action is therefore independent of the pathways for angiotensin II synthesis.
Valsartan does not inhibit ACE (also known as kininase II), which converts Angiotensin I to Angiotensin II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with coughing.

Pharmacokinetics

Valsartan and Amlodipine exhibit linear pharmacokinetics.

Valsartan/Amlodipine combination

Following oral administration of Valsartan/Amlodipine in normal healthy adults, peak plasma concentrations of valsartan and amlodipine are reached in 3 and 6 to 8 hours, respectively. The rate and extent of absorption of valsartan and amlodipine from the combination tablet were the same as when administered as individual tablets. The bio-availabilities of amlodipine and valsartan are not altered by the co-administration of food.

Valsartan

Absorption
Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23%. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (Cmax) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

Distribution
The steady-state volume of distribution of valsartan after intravenous administration is about 17 litres, indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94–97%), mainly serum albumin.

Metabolism
Valsartan is not transformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive.

Excretion
Valsartan shows multiexponential decay kinetics ($t_{½}\alpha$ <1 h and $t_{½}\beta$ about 9 h). Valsartan is primarily eliminated in feces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. 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). The half-life of valsartan is 6 hours.

Amlodipine

Absorption
After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6–12 hours. Absolute bioavailability has been calculated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.

Distribution
Volume of distribution is approximately 21 l/kg. In vitro studies with amlodipine have shown that approximately 97.5% of circulating drug is bound to plasma proteins.

Metabolism
Amlodipine is extensively (approximately 90%) metabolized in the liver to inactive metabolites.

Excretion
Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7–8 days. Ten per cent of original amlodipine and 60% of amlodipine metabolites are excreted in urine.

INDICATIONS

Hypertension
Avsar (amlodipine and valsartan) is indicated in adults whose blood pressure is not adequately controlled on valsartan or amlodipine mono therapy. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.
A patient who experiences dose-limiting adverse reactions on either component Valsartan and Amlodipine alone may be switched to AVSAR containing a lower dose of that component in combination with the other to achieve similar blood pressure reductions. It may also be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.

AVSAR (Valsartan/Amlodipine) may be administered with other anti-hypertensive agents.

DOSAGE AND ADMINISTRATION
The recommended dosage of AVSAR (Valsartan/Amlodipine) is one tablet per day. The usual starting dose is AVSAR 160/5 mg tablet once daily in patients who are not volume-depleted. The dosage can be increased after 1 to 2 weeks of therapy to a maximum of 320 mg of Valsartan and 10 mg of Amlodipine. The majority of the antihypertensive effect is attained within 2 weeks after initiation of therapy or a change in dose.

AVSAR 80/5 mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 5 mg or valsartan 80 mg alone.

AVSAR 160/5 mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 5 mg or valsartan 160 mg alone.

AVSAR 10/160 mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 10 mg or valsartan 160 mg alone or with AVSAR 160/5 mg.
For convenience, patients receiving valsartan and amlodipine from separate dosage forms may be switched to AVSAR tablets containing the same component doses.

Dose adjustment in special populations

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

Hepatic Impairment
Valsartan/Amlodipine is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis. Caution should be exercised when administering Valsartan/Amlodipine combination product to patients with mild to moderate hepatic impairment. In patients with mild to moderate hepatic impairment without cholestasis, the dose of the individual component Valsartan should not exceed 80 mg. Amlodipine dosage recommendations are not well established in patients with mild to moderate hepatic impairment. Exposure to amlodipine is increased in patients with hepatic insufficiency. Limited data is available to suggest initial dose of 2.5 mg of amlodipine in patients with all levels of hepatic impairment, which is not an available strength with AVSAR. When switching eligible hypertensive patients with hepatic impairment to Valsartan/Amlodipine combination, the strength with the lowest available dose of amlodipine component should be used.

Elderly
In elderly patients, caution is required when increasing the dosage. When switching eligible elderly hypertensive patients to AVSAR, the strength with the lowest available dose of the amlodipine component should be used

Administration requirements
AVSAR can be administered as a single dose at any time of day, with or without food. The tablet should be swallowed whole.

CONTRAINDICATIONS
• Known hypersensitivity to the active substances Valsartan or any of the dihydropyridine derivatives including Amlodipine
• Severe hepatic impairment, biliary cirrhosis or cholestasis.
• Concomitant use of Avsar (Valsartan/Amlodipine) with aliskiren or aliskiren-containing products in patients with diabetes mellitus or renal impairment (CrCl <60 ml/min)
• Second and third trimesters of pregnancy
• Severe hypotension.
• Shock (including cardiogenic shock).
• Obstruction of the outflow tract of the left ventricle (e.g. hypertrophic obstructive cardiomyopathy and high grade aortic stenosis)
• Hemodynamically unstable heart failure after acute myocardial infarction

WARNINGS AND PRECAUTIONS

Pregnancy
Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started. (See CONTRAINDICATIONS and USE IN SPECIAL POPULATIONS)
Hypotension
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 with angiotensin receptor blockers. Volume depletion should be corrected prior to administration of Valsartan/Amlodipine and treatment should begin under close medical supervision.
Therapy with Valsartan/Amlodipine should also be initiated with caution 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.
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 Valsartan/Amlodipine, 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 been stabilized.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
There is evidence that the concomitant use of ACE inhibitors, ARBs or aliskiren increases the risk of hypotension, hyperkalemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE inhibitors, ARBs or aliskiren is therefore not recommended. (See DRUG INTERACTIONS)
If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE inhibitors and ARBs should not be used concomitantly in patients with diabetic nephropathy.
Concomitant use of Avsar (Valsartan/Amlodipine) with aliskiren or aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (CrCl <60 ml/min). See CONTRAINDICATIONS

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/Amlodipine. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on Avsar therapy.
No dose adjustment is required in patients with existing mild (CrCl 60 to 90 mL/min) to moderate (CrCl 30 to 60 mL/min) renal impairment. Monitoring of potassium levels and creatinine is advised in moderate renal impairment. Safety and effectiveness of Valsartan/Amlodipine in patients with severe renal impairment (CrCl < 30 mL/min) have not been established.

Renal artery stenosis
Valsartan/Amlodipine should be used with caution to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis to a solitary kidney since blood urea and serum creatinine may increase in such patients.

Kidney Transplantation
To date there is no experience of the safe use of Valsartan/Amlodipine in patients who have had recent kidney transplantation.

Hepatic Impairment
Valsartan is mostly eliminated unchanged via the bile. The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Valsartan/Amlodipine is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis. Caution should be exercised when administering Valsartan/Amlodipine combination product to patients with mild to moderate hepatic impairment. For dosage recommendations of Avsar in hepatic impairment, see DOSAGE AND ADMINISTRATION

Primary hyperaldosteronism
Patients with primary hyperaldosteronism should not be treated with the angiotensin II antagonists such as valsartan, as their renin-angiotensin system is affected by the primary disease.

Angioedema
Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx and/or tongue, has been reported in patients treated with valsartan. Some of these patients previously experienced angioedema with other drugs, including ACE inhibitors. Avsar should be discontinued immediately in patients who develop angioedema and should not be re-administered.

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

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with all other vasodilators, special caution is required with use of Valsartan/Amlodipine in patients suffering from mitral stenosis or significant aortic stenosis or obstructive hypertrophic cardiomyopathy.

Effects on ability to drive and use machines
Patients taking Avsar (Valsartan/Amlodipine) and driving vehicles or using machines should take into account that dizziness or weariness may occasionally occur.
Amlodipine can have mild or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired.

ADVERSE REACTIONS

System organ class	Adverse reactions	Frequency		
		Valsartan/ Amlodipine	Amlodipine	Valsartan
Infections and infestations	Nasopharyngitis	Common	--	--
	Influenza	Common	--	--
Blood and lymphatic system disorders	Hemoglobin and hematocrit decreased	--	--	Not known
	Leukopenia	--	Very rare	--
	Neutropenia	--	--	Not known
	Thrombocytopenia, sometimes with purpura	--	Very rare	Not known
Immune system disorders	Hypersensitivity	Rare	Very rare	Not known
Metabolism and nutrition disorders	Anorexia	Uncommon	--	--
	Hypercalcaemia	Uncommon	--	--
	Hyperglycemia	--	Very rare	--
	Hyperlipidemia	Uncommon	--	--
	Hyperuricaemia	Uncommon	--	--
	Hypokalemia	Common	--	--
	Hyponatraemia	Uncommon	--	--
Psychiatric disorders	Depression	--	Uncommon	--
	Anxiety	Rare	--	--
	Insomnia/sleep disorders	--	Uncommon	--
	Mood swings	--	Uncommon	--
	Confusion	--	Rare	--
Nervous system disorders	Coordination abnormal	Uncommon	--	--
	Dizziness	Uncommon	Common	--
	Dizziness postural	Uncommon	--	--
	Dysgeusia	--	Uncommon	--
	Extrapyramidal syndrome	--	Not known	--
	Headache	Common	Common	--
	Hypertonia	--	Very rare	--
	Paraesthesia	Uncommon	Uncommon	--
	Peripheral neuropathy, neuropathy	--	Very rare	--
	Somnolence	Uncommon	Common	--
	Syncope	--	Uncommon	--
	Tremor	--	Uncommon	--
	Hypoesthesia	--	Uncommon	--
Eye disorders	Visual disturbance	Rare	Uncommon	--
	Visual impairment	Uncommon	Uncommon	--
Ear and labyrinth disorders	Tinnitus	Rare	Uncommon	--
	Vertigo	Uncommon	--	Uncommon
Cardiac disorders	Palpitations	Uncommon	Common	--
	Syncope	Rare	--	--
	Tachycardia	Uncommon	--	--
	Arrhythmias (including bradycardia, ventricular tachycardia, and atrial fibrillation)	--	Very rare	--
	Myocardial infarction	--	Very rare	--
Vascular disorders	Flushing	--	Common	--
	Hypotension	Rare	Uncommon	--
	Orthostatic hypotension	Uncommon	--	--
	Vasculitis	--	Very rare	Not known
Respiratory, thoracic and mediastinal disorders	Cough	Uncommon	Very rare	Uncommon
	Dyspnea	--	Uncommon	--
	Pharyngolaryngeal pain	Uncommon	--	--
	Rhinitis	--	Uncommon	--
Gastrointestinal disorders	Abdominal discomfort, abdominal pain upper	Uncommon	Common	Uncommon
	Change of bowel habit	--	Uncommon	--
	Constipation	Uncommon	--	--
	Diarrhea	Uncommon	Uncommon	--
	Dry mouth	Uncommon	Uncommon	--
	Dyspepsia	--	Uncommon	--
	Gastritis	--	Very rare	--
	Gingival hyperplasia	--	Very rare	--
	Nausea	Uncommon	Common	--
	Pancreatitis	--	Very rare	--
	Vomiting	--	Uncommon	--
Hepatobiliary disorders	Liver function test abnormal, including blood bilirubin increase	--	Very rare*	Not known
	Hepatitis	--	Very rare	--
	Intrahepatic cholestasis, jaundice	--	Very rare	--
Skin and subcutaneous tissue disorders	Alopecia	--	Uncommon	--
	Angioedema	--	Very rare	Not known
	Dermatitis bullous	--	--	Not known
	Erythema	Uncommon	--	--
	Erythema multiforme	--	Very rare	--
	Exanthema	Rare	Uncommon	--
	Hyperhidrosis	Rare	Uncommon	--
	Photosensitivity reaction	--	Uncommon	--
	Pruritus	Rare	Uncommon	Not known
	Purpura	--	Uncommon	--
	Rash	Uncommon	Uncommon	Not known
	Skin discolouration	--	Uncommon	--
	Urticaria and other forms of rash	--	Very rare	--
	Exfoliative dermatitis	--	Very rare	--
	Stevens-Johnson syndrome	--	Very rare	--
	Quincke edema	--	Very rare	--

Musculoskeletal and connective tissue disorders	Arthralgia	Uncommon	Uncommon	--
	Back pain	Uncommon	Uncommon	--
	Joint swelling	Uncommon	--	--
	Muscle spasm	Rare	Uncommon	--
	Myalgia	--	Uncommon	Not known
	Ankle swelling	--	Common	--
	Sensation of heaviness	Rare	--	--
Renal and urinary disorders	Blood creatinine increased	--	--	Not known
	Micturition disorder	--	Uncommon	--
	Nocturia	--	Uncommon	--
	Pollakiuria	Rare	Uncommon	--
	Polyuria	Rare	--	--
	Renal failure and impairment	--	--	Not known
Reproductive system and breast disorders	Impotence	--	Uncommon	--
	Erectile dysfunction	Rare	--	--
	Gynaecomastia	--	Uncommon	--
General disorders and administration site conditions	Asthenia	Common	Uncommon	--
	Discomfort, malaise	--	Uncommon	--
	Fatigue	Common	Common	Uncommon
	Facial edema	Common	--	--
	Flushing, hot flush	Common	--	--
	Non cardiac chest pain	--	Uncommon	--
	Edema	Common	Common	--
	Edema peripheral	Common	--	--
	Pain	--	Uncommon	--
	Pitting edema	Common	--	--
Investigations	Blood potassium increased	--	--	Not known
	Weight increase	--	Uncommon	--
	Weight decrease	--	Uncommon	--

DRUG INTERACTIONS

No drug interaction studies have been conducted with Valsartan/Amlodipine combination product and other drugs, although studies have been conducted with the individual components, valsartan and amlodipine

Amlodipine

CYP3A4 inhibitors
Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring for hypotension and edema is advised and dose adjustment may be required.

CYP3A4 inducers
There is no data available regarding the effect of CYP3A4 inducers (e.g. anticonvulsant agents [carbamazepine, phenobarbital, phenytoin, fosphenytoin, and primidone], rifampicin, Hypericum perforatum) on amlodipine. The concomitant use of CYP3A4 inducers may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

Sildenafil
Monitor for hypotension when sildenafil is co-administered with amlodipine due to additive effects on blood pressure lowering.

Simvastatin
Co-administration of simvastatin with amlodipine increases the systemic exposure of simvastatin. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

Immunosuppressants
Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when co-administered. Frequent monitoring of trough blood levels of cyclosporine and tacrolimus is recommended and dose should be adjusted when appropriate.

Intravenous dantrolene
In animals, lethal ventricular fibrillation and cardiovascular collapse have been observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine should be avoided with intravenous dantrolene in patients with malignant hyperthermia.

Grape fruit juice
Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects.

Valsartan

Non-Steroidal Anti-Inflammatory Drugs and selective COX-II inhibitors
In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration 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 also be attenuated by NSAIDs including selective COX-2 inhibitors.

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

Drugs that are inhibitors of hepatic uptake transporter or hepatic efflux transporter
Valsartan is a substrate of the hepatic uptake transporter OATP1B1 and the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (rifampin, cyclosporine) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.

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. If a diuretic is also used, the risk of lithium toxicity may presumably be increased further with Avsar.

Drugs causing dual blockade of the renin angiotensin aldosterone system (RAAS)
Dual blockade of the RAAS through the combined use of ACE inhibitors, ARBs or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalemia and decreased renal function (including acute renal failure).

USE IN SPECIAL POPULATIONS

Pregnancy

US FDA Pregnancy category D

Valsartan
The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during the first trimester of pregnancy. The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy. 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.

Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is detected, discontinue Avsar as soon as possible and, if appropriate, alternative therapy should be started.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient during the first trimester, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue Avsar, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on 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 Avsar (Valsartan/Amlodipine) should be closely observed for hypotension, oliguria and hyperkalemia.

Amlodipine
The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses. Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and fetus.

Nursing mothers
It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that breast feeding should be discontinued while amlodipine is administered.
It is not known whether valsartan is excreted in human milk. Valsartan was excreted into the milk of lactating rats; however, animal breast milk drug levels may not accurately reflect human breast milk levels. Because many drugs are excreted into human milk and because of the potential for adverse reactions in nursing infants from Valsartan, a decision should be made whether to discontinue nursing or discontinue Avsar, taking into account the importance of the drug to the mother.

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

Elderly (age 65 years or over)
In elderly patients, caution is required when increasing the dosage (See DOSAGE AND ADMINISTRATION)

Renal impairment
The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. There is no apparent correlation between renal function (measured by creatinine clearance) and exposure (measured by AUC) to valsartan in patients with different degrees of renal impairment. 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 <30 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 impairment
Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic impairment have decreased clearance of amlodipine with resulting increase of approximately 40–60% in AUC. On average, in patients with mild to moderate chronic liver disease exposure (measured by AUC values) to valsartan is twice that found in healthy volunteers (matched by age, sex and weight).
Avsar is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis. Caution should be exercised when administering Valsartan/Amlodipine combination product to patients with mild to moderate hepatic impairment. (See DOSAGE AND ADMINISTRATION)

OVER DOSAGE

There is no experience of overdose with Valsartan/Amlodipine combination.

Symptoms
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, dizziness, circulatory collapse, and shock has been reported.

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

Treatment
If ingestion is recent, induction of vomiting or gastric lavage may be considered. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption. Clinically significant hypotension due to Valsartan/Amlodipine overdose calls for active cardiovascular support, including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.
Both valsartan and amlodipine are unlikely to be removed by hemodialysis.

PRESENTATION

AVSAR 80/5mg : Pack of 14 Tablets.
AVSAR 160/5mg : Pack of 14 Tablets.
AVSAR 160/10mg : Pack of 14 Tablets.

INSTRUCTIONS

Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.
Store below 30°C.
For suspected adverse drug reaction, email at reports@pharmevo.biz

For more information on our products call PharmAssist helpline 0800-82222 Monday to Friday 9:00 am to 6:00 pm or email us at : pharmassist@pharmevo.biz

ہدایات:
ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔
تمام دوائیں بچوں کی پہنچ سے دُور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے پر ہی فروخت کی جائے۔
روشنی، گرمی اور نمی سے محفوظ، 30°C سے کم درجہ حرارت پر رکھیں۔
دوا کے ممکنہ منفی اثرات کے متعلق reports@pharmevo.biz پر مطلع کریں۔

ہماری ادویات کی مزید معلومات کے لئے فارم اسسٹ کی ہیلپ لائن نمبر 0800-82222 پر کال کریں۔
پیر تا جمعہ صبح 9:00 بجے تا شام 6:00 بجے
یا ہمیں pharmassist@pharmevo.biz پر ای میل کریں

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DI:AVSR 02 04/2020

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