AVSAR® PLUS ایوسار پلس

[Valsartan+Amlodipine+Hydrochlorothiazide]

COMPOSITION

AVSAR® PLUS 160/5/12.5mg Tablet
Each film coated tablet contains:
Valsartan USP……..160 mg
Amlodipine USP……5 mg (as amlodipine besylate)
Hydrochlorothiazide USP……..12.5 mg
AVSAR® PLUS 160/5/25mg Tablet
Each film coated tablet contains:
Valsartan USP……..160 mg
Amlodipine USP……5 mg (as amlodipine besylate)
Hydrochlorothiazide USP……25 mg
AVSAR® PLUS 160/10/12.5mg Tablet
Each film coated tablet contains:
Valsartan USP……..160 mg
Amlodipine USP……10 mg (as amlodipine besylate)
Hydrochlorothiazide USP……12.5 mg
AVSAR® PLUS 160/10/25mg Tablet
Each film coated tablet contains:
Valsartan USP……..160 mg
Amlodipine USP……10 mg (as amlodipine besylate)
Hydrochlorothiazide USP……..25 mg
AVSAR® PLUS 320/10/25mg Tablet
Each film coated tablet contains:
Valsartan USP……..320 mg
Amlodipine USP……10 mg (as amlodipine besylate)
Hydrochlorothiazide USP……25 mg
(USP Specs.)

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

DESCRIPTION

AVSAR PLUS is a fixed-dose combination of valsartan, amlodipine and hydrochlorothiazide.
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 empirical formula is $C_{24}H_{29}N_5O_3$

Amlodipine is a dihydropyridine 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 $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6SO_3 \cdot H_2O$

Hydrochlorothiazide is a thiazide diuretic. Its chemical name is 6-chloro-3, 4-dihydro-2H-1,2,4-benzothiadiazine-7 sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$

CLINICAL PHARMACOLOGY

Mechanism of Action
The active ingredients of AVSAR PLUS target 3 separate mechanisms involved in blood pressure reduction. The combination of these substances has an additive antihypertensive effect.
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.
Amlodipine
Amlodipine is a dihydropyridine calcium channel blocker 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. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, causing reductions in peripheral vascular resistance and in blood pressure.
Hydrochlorothiazide
Hydrochlorothiazide is a thiazide diuretic. There is a high-affinity receptor in the renal cortex as the primary binding site for the thiazide diuretic action and inhibition of NaCl transport in the distal convoluted tubule. The mode of action of thiazides is through inhibition of the Na+Cl- symporter perhaps by competing for the Cl- site, thereby affecting the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts and indirectly, reducing plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so co-administration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics. The exact mechanism of the antihypertensive effect of thiazides is unknown.

Pharmacokinetics

Amlodipine/valsartan/hydrochlorothiazide
Following oral administration, the rate and extent of absorption of amlodipine, valsartan and hydrochlorothiazide from the combination product are the same as when administered as individual dosage forms.

Valsartan

Absorption
Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23%. Valsartan can 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 biotransformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxy metabolite (valeryl 4-hydroxy valsartan), formed via CYP2C9 iso-enzyme has been identified in plasma at low concentrations (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive.

Elimination
Valsartan shows multi-exponential decay kinetics ($t^{1}/_{4}\alpha$ <1 h and $t^{1}/_{2}\beta$ 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 21L/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.

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

Hydrochlorothiazide

Absorption
The absorption of hydrochlorothiazide, after an oral dose, is rapid (Tmax about 2 hours). The increase in mean AUC is linear and dose proportional in the therapeutic range. The effect of food on HCT absorption, if any, has little clinical significance. Absolute bioavailability of HCT is 70% after oral administration.

Distribution
The apparent volume of distribution is 4-8 L/kg. Circulating hydrochlorothiazide is bound to serum proteins (40-70%), mainly serum albumin. Hydrochlorothiazide also accumulates in erythrocytes at approximately 3times the level in plasma.

Metabolism
Hydrochlorothiazide is eliminated predominantly as unchanged compound.

Elimination
Hydrochlorothiazide is eliminated from plasma with a half-life averaging 6 to 15 hours in the terminal elimination phase. More than 95% of the absorbed dose is being excreted as unchanged compound in the urine. The renal clearance is composed of passive filtration and active secretion into the renal tubule

INDICATIONS

AVSAR PLUS (Valsartan, Amlodipine and Hydrochlorothiazide) is indicated for the treatment of essential hypertension in adults. AVSAR PLUS fixed-dose combination is indicated in patients whose blood pressure is not adequately controlled on valsartan, amlodipine or hydrochlorothiazide monotherapy. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.

This fixed combination drug is not indicated for the initial therapy of hypertension.

DOSAGE AND ADMINISTRATION

General Considerations
The recommended dose of Avsar Plus is one tablet per day, to be taken preferably in the morning. The dosage may be increased after 2 weeks of therapy. The full blood pressure lowering effect is achieved 2 weeks after being on the maximal dose of Avsar Plus. The maximum recommended dose of Avsar Plus is 320/10/25 mg.
Add-on / Switch Therapy
Avsar Plus may be used for patients not adequately controlled on any 2 of the following antihypertensive medication 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 Avsar Plus may be switched to Avsar Plus containing a lower dose of that component to achieve similar blood pressure reductions.
Replacement Therapy
Avsar Plus may be substituted for the individually titrated components

Dosing considerations and dosage adjustment in special populations

Renal impairment
Due to the hydrochlorothiazide component, Avsar Plus is contraindicated for use in patients with anuria and in patients with severe renal impairment [creatinine clearance rate (CrCl) <30 ml/min] or in patients undergoing dialysis. No dose adjustment is required in patients with mild (CrCl 60 to 90 mL/min) or moderate (CrCl 30 to 60 mL/min) renal impairment.
Hepatic impairment
Due to the valsartan component, Avsar Plus is contraindicated in patients with severe hepatic impairment. In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan and therefore Avsar Plus use is not suitable even in this group of patients. Amlodipine dose recommendations have not been established in patients with mild to moderate hepatic impairment. Some data suggests that initial dose of amlodipine in patients with hepatic impairment is 2.5 mg, which is not an available strength with Avsar Plus. When switching eligible hypertensive patients with hepatic impairment to Avsar Plus, the lowest available dose of the amlodipine component should be used. Considering the above recommendations, Avsar Plus use is not suitable in patients with any level of hepatic impairment.

Administration Requirement
For Oral use. AVSAR PLUS can be taken with or without food. The tablets should be swallowed whole with some water, at the same time of the day and preferably in the morning.

CONTRAINDICATIONS

- Hypersensitivity condition to valsartan, amlodipine, hydrochlorothiazide or other sulphonamide or dihydropyridine derivatives.
- Second and third trimesters of pregnancy
- Severe hepatic impairment, biliary cirrhosis or cholestasis.
- Severe renal impairment (creatinine clearance <30ml/min), anuria and patients undergoing dialysis.
- Concomitant use of Avsar Plus with aliskiren-containing products in patients with diabetes mellitus or renal impairment (creatinine clearance <60ml/min)
- Refractory, persistent and treatment resistant hypokalemia, hyponatraemia, hypercalcaemia, and symptomatic hyperuricaemia.
- 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).
- Haemodynamically unstable heart failure after acute myocardial infarction.

WARNINGS AND PRECAUTIONS

Fetal Toxicity
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 Avsar Plus as soon as possible. Avsar Plus use is not recommended in the first trimester of pregnancy and contraindicated in the second and third trimesters. See USE IN SPECIAL POPULATIONS

Hypotension in volume or salt depleted patients
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/amlodipine/HCT, or the treatment should start under close medical supervision. If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, given an IV 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.

Renal impairment
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/HCT. Monitor renal function periodically in these patients.
Thiazide diuretics may also precipitate azotemia in patients with existing chronic kidney disease. When Avsar Plus is used in patients with renal impairment. periodic monitoring of serum electrolytes (including potassium), creatinine and uric acid serum levels is recommended. Avsar Plus is contraindicated in patients with severe renal impairment, anuria or undergoing dialysis. No dose adjustment of Avsar Plus is required for patients with mild to moderate renal impairment (CrCl ≥30ml/min)

Renal artery stenosis
Avsar Plus should be used with caution 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
There is currently no experience on the safe use of Valsartan/amlodipine/HCT in patients who have recently undergone kidney transplantation.

Primary hyperaldosteronism
Patients with primary hyperaldosteronism should not be treated with Valsartan as their renin-angiotensin system is not activated. Therefore, Avsar Plus is not recommended in this population.

Hepatic impairment
Use of Valsartan is contraindicated in severe hepatic impairment, biliary cirrhosis and cholestasis. Use of Avsar Plus is not suitable in patients with mild-to-moderate liver disease. See DOSAGE AND ADMINISTRATION and USE IN SPECIAL POPULATIONS. Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

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 taking valsartan. Avsar Plus should be immediately discontinued in patients who develop angioedema, and should not be re-administered.

Heart failure/coronary artery disease/post-myocardial infarction:
In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin antagonists including Valsartan has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Evaluation of such patients with heart failure or post-myocardial infarction should always include assessment of renal function.

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. Amlodipine has also been associated with increased reports of pulmonary edema in patients with congestive heart failure.

Caution is advised in patients with congestive heart failure and coronary artery disease particularly at the maximum dose of 320/10/25 mg.

Serum electrolyte changes
Some patients with heart failure have developed increases in potassium on Valsartan. These effects are usually minor and transient, and occur more commonly in patients with pre-existing renal impairment or patients taking other concomitant drugs known to increase potassium levels. Dosage reduction and/or discontinuation of therapy may be required.

Hydrochlorothiazide can cause hypokalemia and hypochloroaemic alkalosis or hyponatremia. Hyponatraemia may be accompanied by neurological symptoms (nausea, progressive disorientation, apathy) and in severe cases may require discontinuation of therapy. Hypomagnesaemia can result in hypokalemia which appears difficult to treat despite potassium repletion. HCT should be administered with caution in patients with conditions involving enhanced potassium loss, for example salt-losing nephropathies and prerenal (cardiogenic) impairment of kidney function. If hypokalemia is accompanied by clinical signs (e.g., muscular weakness, paresis, or ECG alterations), Avsar Plus should be discontinued. Correction of hyponatremia, hypokalemia, and any coexisting hypomagnesaemia is recommended prior to the initiation of Avsar Plus.

In some patients, the counteracting effects of valsartan and HCT on serum potassium may approximately balance each other. All patients receiving Avsar Plus should be periodically monitored for imbalances in electrolytes, particularly potassium, sodium and magnesium.

Hydrochlorothiazide decreases urinary calcium excretion and may cause elevations of serum calcium. Also monitor calcium levels in patients with hypercalcemia receiving Avsar Plus.

Hypersensitivity Reactions
Hypersensitivity reactions to HCT 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 Erythematous
Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematous.

Aortic and mitral valve stenosis
As with all other vasodilators, special caution is indicated with use of Valsartan in patients suffering from aortic or mitral stenosis due to its potential vaso-dilatory effect.

Metabolic Imbalances
Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides. In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required.

Hyperuricemia and gout
Hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricemia and precipitate gout in susceptible patients.

Photosensitivity
Cases of photosensitivity reactions have been reported with thiazide diuretics. If photosensitivity reaction occurs during treatment with Avsar Plus, treatment should be stopped. If a re-administration is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

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

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. 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. See CONTRAINDICATIONS

Effects on ability to drive and use machines
Patients taking Avsar Plus 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 Avsar Plus suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired.

ADVERSE REACTIONS

System Organ Class	Adverse reactions	Frequency			
		Valsartan/amlodipine/HCT	Amlodipine	Valsartan	HCTZ
Blood and lymphatic system disorders	Agranulocytosis, bone marrow failure	-	-	-	Very rare
	Hemoglobin and Hematocrit decreased	-	-	Not known	-
	Hemolytic anemia	-	-	-	Very rare
	Leukopenia	-	Very rare	-	Very rare
	Neutropenia	-	-	Not known	-
	Thrombocytopenia sometimes with purpura	-	Very rare	Not known	Rare
	Aplastic anemia	-	-	-	Not known
Immune system disorders	Hypersensitivity	-	Very rare	Not known	Very rare
Metabolism and nutrition disorders	Anorexia	Uncommon	-	-	-
	Hypercalcaemia	Uncommon	-	-	Rare
	Hyperglycemia	-	Very rare	-	Rare
	Hyperlipidemia	Uncommon	-	-	-
	Hyperuricaemia	Uncommon	-	-	Common
	Hypochloraemic alkalosis	-	-	-	Very rare
	Hypokalemia	Common	-	-	Very common
	Hypomagnesaemia	-	-	-	Common
	Hyponatraemia	Uncommon	-	-	Common
	Worsening of Diabetic metabolic state	-	-	-	Rare
Psychiatric disorders	Depression	-	Uncommon	-	Rare
	Insomnia/sleep disorders	Uncommon	Uncommon	-	Rare
	Mood swings	-	Uncommon	-	-
	Confusion	-	Rare	-	-
Nervous system disorders	Coordination abnormal	Uncommon	-	-	-
	Dizziness	Common	Common	-	Rare
	Dysgeusia	Uncommon	Uncommon	-	-
	Extrapyramidal syndrome	-	Not known	-	-
	Headache	Common	Common	-	Rare
	Hypertonia	-	Very rare	-	-

	Lethargy	Uncommon	-	-	-
	Paraesthesia	Uncommon	Uncommon	-	Rare
	Peripheral neuropathy, neuropathy	Uncommon	Very rare	-	-
	Somnolence	Uncommon	Common	-	-
	Syncope	Uncommon	Uncommon	-	-
	Tremor	-	Uncommon	-	-
	Hypoesthesia	-	Uncommon	-	-
Eye disorders	Acute angle-closure glaucoma	-	-	-	Not known
	Visual disturbance	-	Uncommon	-	-
	Visual impairment	Uncommon	Uncommon		Rare
Ear and labyrinth disorders	Tinnitus	-	Uncommon	-	-
	Vertigo	Uncommon	-	Uncommon	-
Cardiac disorders	Palpitations	-	common	-	-
	Tachycardia	Uncommon	-	-	-
	Arrhythmias (including bradycardia, ventricular tachycardia, and atrial fibrillation)	-	Very rare		Rare
	Myocardial infarction	-	Very rare	-	-
Vascular disorders	Flushing	-	Common	-	-
	Hypotension	Common	Uncommon	-	-
	Orthostatic hypotension	Uncommon	-	-	Common
	Phlebitis, thrombophlebitis	Uncommon	-	-	-
	Vasculitis	-	Very rare	Not known	-
Respiratory, thoracic and mediastinal disorders	Cough	Uncommon	Very rare	Uncommon	
	Dyspnea	Uncommon	Uncommon	-	-
	Respiratory distress, pulmonary edema, pneumonitis	-	-	-	Very rare
	Rhinitis	-	Uncommon		
	Throat irritation	Uncommon	-	-	-
Gastro intestinal disorders	Abdominal discomfort, abdominal pain upper	Uncommon	Common	Uncommon	Rare
	Breath odour	Uncommon	-	-	-
	Change of bowel habit	-	Uncommon	-	-
	Constipation	-	-	-	Rare
	Decreased appetite	-	-	-	Common
	Diarrhea	Uncommon	Uncommon	-	Rare
	Dry mouth	Uncommon	Uncommon	-	-
	Dyspepsia	Common	Uncommon	-	-
	Gastritis	-	Very rare	-	-
	Gingival hyperplasia	-	Very rare	-	-
	Nausea	Uncommon	Common	-	Common
	Pancreatitis	-	Very rare	-	Very rare
	Vomiting	Uncommon	Uncommon	-	Common
Hepatobiliary disorders	Liver function test abnormal, including blood bilirubin increase	-	Very rare	Not known	-
	Hepatitis	-	Very rare	-	-
	Intrahepatic cholestasis, jaundice	-	Very rare	- -	Rare
Skin & sub-cutaneous tissue disorders	Alopecia	-	Uncommon	-	-
	Angioedema	-	Very rare	Not known	-
	Dermatitis bullous	-	-	Not known	-
	Cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus	-	-	-	Very rare
	Erythema multiforme	-	Very rare	-	Not known
	Exanthema	-	Uncommon	-	-
	Hyperhidrosis	Uncommon	Uncommon	-	Rare
	Photosensitivity reaction	-	Very rare	-	Rare
	Pruritus	Uncommon	Uncommon	Not known	-
	Purpura	-	Uncommon	-	Rare
	Rash	-	Uncommon	Not known	Common
	Skin discoloration	-	Uncommon	-	
	Urticaria and other forms of rash	-	Very rare	-	Common
	Vasculitis necrotising and toxic epidermal necrolysis	-	-	-	Very rare
	Exfoliative dermatitis	-	Very rare	-	-
	Stevens-Johnson syndrome	-	Very rare	-	-
	Quincke edema	-	Very rare	-	-
Musculo skeletal and connective tissue disorders	Arthralgia	-	Uncommon	-	-
	Back pain	Uncommon	Uncommon	-	-
	Joint swelling	Uncommon	-	-	-
	Muscle spasm	Uncommon	Uncommon	-	Not known
	Muscular weakness	Uncommon	-	-	-
	Myalgia	Uncommon	Uncommon	Not known	-
	Pain in extremity	Uncommon	-	-	-
	Ankle swelling	-	Common	-	-
Renal and urinary disorders	Blood creatinine increased	Uncommon	-	Not known	-
	Micturition disorder		Uncommon	-	-
	Nocturia	-	Uncommon	-	-
	Pollakiuria	Common	Uncommon	-	--
	Renal dysfunction	-	-	-	Not known
	Acute renal failure	Uncommon	-	-	Not known
	Renal failure and impairment	-		Not known	Rare
Reproductive system and breast disorders	Impotence	Uncommon	Uncommon	-	common
	Gynaecomastia	-	Uncommon	-	-
General disorders and administration site conditions	Abasia, gait disturbance	Uncommon	-	-	-
	Asthenia	Uncommon	Uncommon	-	-
	Discomfort, malaise	Uncommon	Uncommon	-	Not known
	Fatigue	common	common	Uncommon	
	Non cardiac chest pain	uncommon	uncommon	-	-
	Edema	common	common	-	-
	Pain	-	uncommon	-	-
	Pyrexia	-	-	-	Not known
Investigations	Lipids ↑	-	-	-	Very common
	Blood urea nitrogen ↑	Uncommon	-	-	-
	Blood uric acid ↑	Uncommon	-	-	-
	Glycosuria	-	-	-	rare
	Blood potassium ↓	Uncommon	-	-	-
	Blood potassium ↑	-	-	Not known	-
	Weight increase	Uncommon	uncommon	-	-
	Weight decrease	-	Uncommon	-	-

DRUG INTERACTIONS

No formal interaction studies with other drugs have been performed with the triple combination product Valsartan/Amlodipine/Hydrochlorothiazide. Only information on interactions with other drugs that are known for the individual active substances is given below:

Amlodipine

CYP3A4 Inhibitors
Co-administration with moderate and strong CYP3A4 inhibitors (protease inhibitors: ritonavir, azole antifungals: ketoconazole or itraconazole, macrolides: erythromycin or clarithromycin, verapamil or diltiazem) results in increased systemic exposure to amlodipine and may require dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A4 inhibitors to determine the need for dose adjustment.
CYP3A4 Inducers
No information is available on the quantitative effects of CYP3A4 inducers on amlodipine. Concomitant use of CYP3A4 inducers (e.g. anticonvulsants: carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone; rifampicin and Hypericum perforatum) may give a lower plasma concentration of amlodipine. Blood pressure should be closely monitored when amlodipine is co-administered with CYP3A4 inducers.
Sildenafil
Monitor for hypotension when sildenafil is co-administered with amlodipine
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
Dantrolene infusion
In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and IV dantrolene. Due to risk of hyperkalemia, co-administration of calcium channel blockers such as amlodipine with IV dantrolene should be avoided in patients with malignant hyperthermia
Grape fruit
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

Potassium supplements and drugs known to increase potassium levels
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 advisable.
Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 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, including valsartan, may result in deterioration of renal function, including possible acute renal failure and an increase in serum potassium. 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.
Inhibitors of hepatic uptake/efflux transporters
Valsartan is a substrate of the hepatic uptake transporter OATP1B1 and of the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.
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. In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function, and electrolytes in patients on Avsar Plus and other agents that affect the RAS. Do not co-administer aliskiren with Avsar Plus in patients with diabetes or in patients with renal impairment (creatinine clearance <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. Monitor lithium levels in patients taking Avsar Plus.

Hydrochlorothiazide

Anti-diabetic drugs (oral agents and insulin)
Thiazides may alter glucose tolerance. Dosage adjustment of the anti-diabetic drug may be required. Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.
Non-steroidal anti-inflammatory drugs (NSAIDs and COX-2 selective inhibitors)
NSAIDS can attenuate the antihypertensive effect of hydrochlorothiazide when administered simultaneously.
Drugs known to cause hyponatremia
The hyponatraemic effect of diuretics may be intensified by concomitant administration of antidepressants, antipsychotics, antiepileptics such as carbamazepine, etc. Caution is indicated in long-term administration of these drugs.
Bile acid sequestrants
Absorption of thiazide diuretics, including hydrochlorothiazide, is decreased by cholestyramine or colestipol. Staggering the dosage of HCT and ion exchange resins (e.g., cholestyramine, colestipol) such that HCT is administered at least 4 hours before or 4 to 6 hours after the administration of resins would potentially minimize the interaction.
Cyclosporine
Concomitant treatment of HCT with cyclosporine may increase the risk of hyperuricemia and gout-type complications
Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with thiazides. Since renal clearance of lithium is reduced by thiazides, the risk of lithium toxicity may presumably be increased further with the triple combination Avsar Plus, due to its valsartan component. Therefore, careful monitoring of serum lithium concentrations is recommended during concomitant use.
Alcohol, barbiturates or narcotics
Concomitant administration of thiazide diuretics with substances that also have a blood pressure lowering effect (e.g. by reducing sympathetic central nervous system activity or direct vasodilatation) may potentiate orthostatic hypotension.
Amantadine
Thiazides, including HCT may increase the risk of adverse reactions caused by amantadine.
Anticholinergic agents and drugs affecting gastric motility
The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden); apparently due to a decrease in GI motility and stomach emptying rate. Conversely, it is anticipated that prokinetic substances such as itopride may decrease the bioavailability of thiazide-type diuretics.
Beta blockers and diazoxide
Concomitant use of thiazide diuretics, including HCT with beta blockers or diazoxide may increase the risk of hyperglycemia.
Cytotoxic agents
Thiazides, including HCT, may reduce the renal excretion of cytotoxic agents (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.
Digitalis glycosides
Thiazide-induced hypokalemia or hypomagnesaemia may occur with HCT, favouring the onset of digitalis-induced cardiac arrhythmias. Caution is advised with careful monitoring of serum electrolyte levels
Iodine contrasting agents
In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of iodine products. Patients should be re-hydrated before the administration.
Drugs affecting serum potassium level
The hypokalemic effect of hydrochlorothiazide may be increased by concomitant administration of kaliuretic diuretics, corticosteroids, laxatives, adrenocorticotropic hormone (ACTH), amphotericin, carbenoxolone, penicillin G and salicylic acid derivatives or antiarrhythmics. If these drugs are to be prescribed with the amlodipine /valsartan /HCT combination, monitoring of potassium plasma levels is advised.
Drugs that could induce torsades de pointes
Due to the risk of hypokalemia, HCT should be administered with caution when used with drugs that could induce torsades de pointes, in particular Class Ia and Class III antiarrhythmics and some antipsychotics.
Gout Medications (probenecid, sulfinpyrazone and allopurinol)
Dose adjustment of uricosuric drugs may be necessary as HCT may raise the level of serum uric acid. Increase of dose of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics, including HCT, may also increase the incidence of hypersensitivity reactions to allopurinol.
Methyldopa
There have been isolated reports of hemolytic anemia occurring with concomitant use of hydrochlorothiazide and methyldopa.
Non-depolarising skeletal muscle relaxants (e.g. tubocurarine)
Thiazides, including hydrochlorothiazide, potentiate the action of curare derivatives.
Vitamin D and calcium salts
Administration of thiazide diuretics, including HCT, with vitamin D or with calcium salts may potentiate the rise in serum calcium. Concomitant use of thiazide type diuretics may lead to hypercalcaemia in patients pre-disposed for hypercalcaemia (e.g. hyperparathyroidism, malignancy or vitamin-D-mediated conditions) by increasing tubular calcium reabsorption

USE IN SPECIAL POPULATIONS

Pregnancy
US FDA pregnancy category D. The safety of amlodipine in human pregnancy has not been established. 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. Hydrochlorothiazide crosses the placenta; its use during the second and third trimester may compromise feto-placental perfusion and may cause fetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia. There is limited pregnancy experience with HCT during the first trimester.

The use of Avsar Plus is not recommended during first trimester and contra-indicated during the second and third trimester of pregnancy. When pregnancy is detected, discontinue Avsar Plus as soon as possible. In the unusual case, of no appropriate alternative therapy, 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 Plus, unless it is considered lifesaving for the mother. If exposure to AIIRAs has occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken AIIRAs should be closely observed for hypotension.

Nursing mothers
No information is available regarding the use of valsartan and/or amlodipine during breast-feeding. Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses cause intense diuresis that can inhibit milk production. The use of Avsar Plus during breast-feeding is not recommended. If Avsar Plus is used during breast-feeding, doses should be kept as low as possible. Alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Pediatrics
The safety and effectiveness of Avsar Plus in pediatric patients have not been established.

Elderly (age 65 years or over)
In elderly patients, amlodipine clearance tends to decline, causing increases in (AUC) and elimination half-life while mean systemic AUC of valsartan is higher by 70% than in the young. Caution including more frequent monitoring of blood pressure, low initial dose and slower dose titration is recommended in elderly patients.

Renal impairment
The pharmacokinetics of amlodipine is not significantly influenced by renal impairment while no correlation was seen between renal function and systemic exposure to valsartan. In the presence of renal impairment, mean peak plasma levels and AUC values of HCT are increased and the urinary excretion rate is reduced. In patients with mild to moderate renal impairment, a 3-fold increase in hydrochlorothiazide AUC has been observed and in severe renal impairment an 8-fold increase in AUC has been observed. Safety and effectiveness of Avsar Plus 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 to90 mL/min) or moderate (CrCl 30 to 60 mL/min) renal impairment.

Hepatic impairment
Exposure to amlodipine is increased in patients with hepatic insufficiency. 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). Due to the valsartan component, Avsar Plus is contraindicated in patients with severe hepatic impairment. See DOSAGE AND ADMINISTRATION.

OVER DOSAGE

Symptoms
There is no experience of overdose with the triple combination Valsartan/amlodipine/HCT. The major symptom of overdose with Valsartan is possibly pronounced hypotension with dizziness. Overdose with amlodipine may result in excessive peripheral vasodilation and, possibly, reflex tachycardia. Marked and potentially prolonged systemic hypotension, including shock with fatal outcome, has been reported with amlodipine. Most common signs and symptoms observed with HCT overdose are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis

Treatment
Clinically significant hypotension due to 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. Amlodipine and valsartan are unlikely to be removed by hemodialysis. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

PRESENTATION

AVSAR® PLUS 160/5/12.5mg : Pack of 28 Tablets
AVSAR® PLUS 160/5/25mg : Pack of 28 Tablets
AVSAR® PLUS 160/10/12.5mg : Pack of 28 Tablets
AVSAR® PLUS 160/10/25mg : Pack of 28 Tablets
AVSAR® PLUS 320/10/25mg : Pack of 28 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 heat, light and moisture.
Store below 30°C.

For more information on our products
call PharmAssist helpline 0800-82222
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