Valam-H™

(Amlodipine + Valsartan + Hydrochlorothiazide) Tablet

ویلم-ایچ

Valam-H Plus™

(Amlodipine + Valsartan + Hydrochlorothiazide) Tablet

ویلم-ایچ پلس

COMPOSITION:

Valam-H Tablet 5/160/12.5 mg:
Each film coated tablet contains:
Amlodipine (as Besilate) ..... 5 mg.
Valsartan ..... 160 mg.
Hydrochlorothiazide ..... 12.5 mg.

Product Specs.: USP

Valam-H Tablet 5/160/25 mg:
Each film coated tablet contains:
Amlodipine (as Besilate) ..... 5 mg.
Valsartan ..... 160 mg.
Hydrochlorothiazide ..... 25 mg.

Product Specs.: USP

Valam-H Tablet 10/160/12.5 mg:
Each film coated tablet contains:
Amlodipine (as Besilate) ..... 10 mg.
Valsartan ..... 160 mg.
Hydrochlorothiazide ..... 12.5 mg.

Product Specs.: USP

Valam-H Tablet 10/160/25 mg:
Each film coated tablet contains:
Amlodipine (as Besilate) ..... 10 mg.
Valsartan ..... 160 mg.
Hydrochlorothiazide ..... 25 mg.

Product Specs.: USP

Valam-H Plus Tablet 10/320/25 mg:
Each film coated tablet contains:
Amlodipine (as Besilate) ..... 10 mg.
Valsartan ..... 320 mg.
Hydrochlorothiazide ..... 25 mg.

Product Specs.: USP

DESCRIPTION:
Valam-H is a fixed combination of amlodipine, valsartan, and hydrochlorothiazide. contains the besylate salt of amlodipine, a dihydropyridine calcium channel blocker (CCB). Amlodipine besylate, USP is a white to pale yellow crystalline powder, slightly soluble in water and sparingly soluble in ethanol. Amlodipine besylate's chemical name is 3-Ethyl 5-methyl(±)-2-[(2-aminoethoxy)methyl]-4-(o-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulfonate Hydrochlorothiazide, USP is a white, or practically white, practically odorless, crystalline powder. It is slightly soluble in water; freely soluble in sodium hydroxide solution, in n-butylamine, and in dimethylformamide; sparingly soluble in methanol; and insoluble in ether, in chloroform, and in dilute mineral acids. Hydrochlorothiazide is chemically described as 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7- sulfonamide 1,1-dioxide. Hydrochlorothiazide is a thiazide diuretic.

CLINICAL PHARMACOLOGY:
Mechanism of Action: The active ingredients target 3 separate mechanisms involved in blood pressure regulation. Specifically, amlodipine blocks the contractile effects of calcium on cardiac and vascular smooth muscle cells; valsartan blocks the vasoconstriction and sodium retaining effects of angiotensin II on cardiac, vascular smooth muscle, adrenal and renal cells; and hydrochlorothiazide directly promotes the excretion of sodium and chloride in the kidney leading to reductions in intravascular volume.
Pharmacodynamics:
Amlodipine: Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic oral administration of amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.
Valsartan: Valsartan inhibits the pressor effect of angiotensin II infusions. An oral dose of 80 mg inhibits the pressor effect by about 80% at peak with approximately 30% inhibition persisting for 24 hours. No information on the effect of larger doses is available. Removal of the negative feedback of angiotensin II causes a 2- to 3-fold rise in plasma renin and consequent rise in angiotensin II plasma concentration in hypertensive patients. Minimal decreases in plasma aldosterone were observed after administration of valsartan; very little effect on serum potassium was observed. Administration of valsartan to patients with essential hypertension results in a significant reduction of sitting, supine, and standing systolic blood pressure, usually with little or no orthostatic change.
Hydrochlorothiazide: After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.
Pharmacokinetics:
Following oral administration in normal healthy adults, peak plasma concentrations of amlodipine, valsartan and HCTZ are reached in about 6 hours, 3 hours, and 2 hours, respectively. The rate and extent of absorption of amlodipine, valsartan and HCTZ are the same as when administered as individual dosage forms. The bioavailability of amlodipine, valsartan, and HCTZ were not altered was administered with food. may be administered with or without food. Amlodipine Peak plasma concentrations of amlodipine are reached 6 to 12 hours after administration of amlodipine alone. Absolute bioavailability has been estimated to be between 64% and 90%. The apparent volume of distribution of amlodipine is 21 L/kg. Approximately 93% of circulating amlodipine is bound to plasma proteins in hypertensive patients. Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine. Elimination of amlodipine from the plasma is biphasic with a terminal elimination half-life of about 30 to 50 hours. Steady state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.
Valsartan: Following oral administration of valsartan alone peak plasma concentrations of valsartan are reached in 2 to 4 hours. Absolute bioavailability is about 25% (range 10% to 35%). The steady state volume of distribution of valsartan after intravenous administration is 17 L indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (95%), mainly serum albumin. Valsartan shows biexponential decay kinetics following intravenous administration with an average elimination half-life of about 6 hours. The recovery is mainly as unchanged drug, with only about 20% of dose recovered as metabolites. The primary metabolite, accounting for about 9% of dose, is valeryl 4-hydroxy valsartan. In vitro metabolism studies involving recombinant CYP450 enzymes indicated that the CYP2C9 isoenzyme is responsible for the formation of valeryl-4-hydroxy valsartan. Valsartan does not inhibit CYP450 isozymes at clinically relevant concentrations. CYP450 mediated drug interaction between valsartan and coadministered drugs are unlikely because of the low extent of metabolism. Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance).
Hydrochlorothiazide: The estimated absolute bioavailability of hydrochlorothiazide after oral administration is about 70%. Peak plasma hydrochlorothiazide concentrations (C_{max}) are reached within 2 to 5 hours after oral administration. There is no clinically significant effect of food on the bioavailability of hydrochlorothiazide. Hydrochlorothiazide binds to albumin (40% to 70%) and distributes into erythrocytes. Following oral administration, plasma hydrochlorothiazide concentrations decline biexponentially, with a mean distribution half-life of about 2 hours and an elimination half-life of about 10 hours. About 70% of an orally administered dose of hydrochlorothiazide is eliminated in the urine as unchanged drug.

SPECIAL POPULATIONS:
Geriatric: Elderly patients have decreased clearance of amlodipine with a resulting increase in peak plasma levels, elimination half-life, and AUC. 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. Limited amount of data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.
Gender. Pharmacokinetics of valsartan do not differ significantly between males and females.
Race: Pharmacokinetic differences due to race have not been studied.
Renal insufficiency: The pharmacokinetics of amlodipine are 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. Valsartan has not been studied in patients with severe impairment of renal function (creatinine clearance <10 mL/min). Valsartan is not removed from the plasma by hemodialysis.
Hepatic insufficiency: Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40% to 60%. On average, patients with mild-to-moderate chronic liver disease have twice the exposure (measured by AUC values) to valsartan of healthy volunteers (matched by age, sex, and weight).

DRUG INTERACTIONS:
Amlodipine: In vitro data in human plasma indicate that amlodipine has no effect on the protein binding of digoxin, phenytoin, warfarin, and indomethacin. Impact of other drugs on amlodipine co-administered cimetidine, magnesium-and aluminum hydroxide antacids, sildenafil, and grapefruit juice have no impact on the exposure to amlodipine. CYP3A.
inhibitors: Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers did not significantly change amlodipine systemic exposure. However, strong inhibitors of CYP3A (e.g., itraconazole, clarithromycin) may increase the plasma concentrations of amlodipine to a greater extent.
Hydrochlorothiazide:
Drugs that alter gastrointestinal motility: The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g., atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate. Conversely, pro-kinetic drugs may decrease the bioavailability of thiazide diuretics.
Cholestyramine: In a dedicated drug interaction study, administration of cholestyramine 2 hours before hydrochlorothiazide resulted in a 70% reduction in exposure to hydrochlorothiazide. Further, administration of hydrochlorothiazide 2 hours before cholestyramine resulted in 35% reduction in exposure to hydrochlorothiazide.
Antineoplastic agents (e.g., cyclophosphamide, methotrexate): Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects.
Alcohol, barbiturates, or narcotics: Potentiation of orthostatic hypotension may occur.
Skeletal muscle relaxants: Possible increased responsiveness to muscle relaxants such as curare derivatives.

INDICATION & USAGE:
Amlodipine, valsartan, hydrochlorothiazide is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than 1 drug to achieve blood pressure goals.
DOSAGE & ADMINISTRATION:
General Considerations Dose once-daily. The dosage may be increased after 2 weeks of therapy. The full blood pressure lowering effect was achieved 2 weeks after being on the maximal dose.
The maximum recommended dose is 10/320/25 mg.
Add-on/Switch Therapy may be used for patients not adequately controlled on any 2 of the following antihypertensive classes: calcium channel blockers, angiotensin receptor blockers, and diuretics. A patient who experiences dose-limiting adverse reactions to an individual component while on any dual combination of the components may be switched to a lower dose of that component to achieve similar blood pressure reductions.
Replacement therapy: may be substituted for the individually titrated components.
Use with other antihypertensive drug: may be administered with other antihypertensive agents.

CONTRAINDICATIONS:
Do not use in patients with anuria, hypersensitivity to other sulfonamide-derived drugs, or hypersensitivity to any component of this product. Do not co administer aliskiren in patients with diabetes.

WARNINGS & PRECAUTIONS:
Fetal Toxicity:
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 as soon as possible.
Hypotension in volume- or salt-Depleted patients: According to innovators data Excessive hypotension, including orthostatic hypotension, was seen in 1.7% of patients treated with the maximum dose (10/320/25 mg) compared to 1.8% of valsartan/HCTZ (320/25 mg) patients, 0.4% of amlodipine/valsartan (10/320 mg) patients, and 0.2% of HCTZ/amlodipine (25/10 mg) patients in a controlled trial in patients with moderate to severe uncomplicated hypertension.
Increased angina and/or myocardial infarction: 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.
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.Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function.
Potassium abnormalities: In the controlled trial of in moderate to severe hypertensive patients, the incidence of hypokalemia (serum potassium <3.5 mEq/L) at any time post-baseline with the maximum dose of HCT (10/320/25 mg) was 10% compared to 25% with HCTZ/amlodipine (25/10 mg), 7% with valsartan/HCTZ (320/25 mg), and 3% with amlodipine/valsartan (10/320 mg).One patient (0.2%) discontinued therapy due to an adverse event of hypokalemia in each of the and HCTZ/amlodipine groups. The incidence of hyperkalemia (serum potassium >5.7 mEq/L) was 0.4% with Valam H compared to 0.2% to 0.7% with the dual therapies.
Hypersensitivity reaction: Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history. Systemic Lupus Erythematosus Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.Lithium Interaction Increases in serum lithium concentrations and lithium toxicity have been reported with concomitant use of valsartan or thiazide diuretics. Monitor lithium levels in patients receiving lithium
Metabolic imbalances: Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides. 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. Hydrochlorothiazide decreases urinary calcium excretion and may cause elevations of serum calcium. Monitor calcium levels in patients with hypercalcemia.
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 occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible.

DRUG INTERACTIONS:
Impact of other drugs on amlodipine:
CYP3A Inhibitors: Co-administration with CYP3A inhibitors (moderate and strong) 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 CYP3A inhibitors to determine the need for dose adjustment. Blood pressure should be closely monitored when amlodipine is co-administered with CYP3A 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.
Immunosuppressant's: 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 adjust the dose when appropriate.
Valsartan: No clinically significant pharmacokinetic interactions were observed when valsartan was co-administered with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. The valsartan-atenolol combination was more antihypertensive than either component, but it did not lower the heart rate more than atenolol alone.Co-administration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.
Potassium: 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 (COX-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 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.
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 other agents that affect the RAS.
Lithium: Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists or thiazides. Monitor lithium levels in patients taking this combination.
Use in Specific population:
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 as soon as possible.
Nursing mothers: It is not known whether amlodipine and valsartan are excreted in human milk, but thiazides are excreted in human milk and valsartan is excreted in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.
Pediatric use: The safety and effectiveness in pediatric patients have not been established
Geriatric use amlodipine: Clinical studies of amlodipine besylate tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects
Renal impairment: Safety and effectiveness of Valam H 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) or moderate (CrCl 30 to 60 mL/min) renal impairment.
Hepatic impairment: Exposure to amlodipine is increased in patients with hepatic insufficiency, The recommended initial dose of amlodipine in patients with hepatic impairment is 2.5 mg, which is not an available strength
Valsartan: No dose adjustment is necessary for patients with mild-to-moderate disease. No dosing recommendations can be provided for patients with severe liver disease.
Hydrochlorothiazide: Minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.
Adverse reactions: Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.
Amlodipine: Gynecomastia has been reported infrequently and a causal relationship is uncertain. Jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalization, have been reported in association with use of amlodipine.
Valsartan:
The following additional adverse reactions have been reported in postmarketing experience with valsartan or valsartan/hydrochlorothiazide:
Blood and lymphatic:
Decrease in hemoglobin, decrease in hematocrit, neutropenia hypersensitivity: There are rare reports of angioedema.Some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Should not be re-administered to patients who have had angioedema.
Digestive: Elevated liver enzymes and very rare reports of hepatitis
Renal: Impaired renal function, renal failure
Clinical Laboratory tests: Hyperkalemia
Dermatologic: Alopecia, bullous dermatitis
Vascular: Vasculitis
Nervous system: Syncope Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.
Hydrochlorothiazide: The following additional adverse reactions have been reported in postmarketing experience with hydrochlorothiazide:
Acute renal failure, renal disorder, aplastic anemia, erythema multiforme, pyrexia, muscle spasm, asthenia, acute angle-closure glaucoma, bone marrow failure, worsening of diabetes control, hypokalemia, blood lipids increased, hyponatremia, hypomagnesemia, hypercalcemia, hypochloremic alkalosis, impotence, visual impairment. Pathological changes in the parathyroid gland of patients with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. If hypercalcemia occurs, further diagnostic evaluation is necessary.
Hydrochlorothiazide:
When administered concurrently the following drugs may interact with thiazide diuretics:
Antidiabetic drugs (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be required.
Non-steroidal anti-inflammatory drugs (NSAIDs and COX-2 selective inhibitors): When combination and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of diuretic is obtained.
Carbamazepine:
May lead to symptomatic hyponatremia. Ion exchange resins: Staggering the dosage of hydrochlorothiazide and ion exchange resins (e.g., cholestyramine, colestipol) such that hydrochlorothiazide 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 with cyclosporine may increase the risk of hyperuricemia and gout-type complications.

OVER DOSAGE:
Limited data are available related to over dosage in humans. The most likely manifestations of over dosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

INSTRUCTIONS:
- Store below 30ºC.
- Protect from heat, sunlight & moisture.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:

Valam-H tablet 5/160/12.5 mg	:	Pack of 4 x 7 tablets.
Valam-H tablet 5/160/25 mg	:	Pack of 4 x 7 tablets.
Valam-H tablet 10/160/12.5 mg	:	Pack of 4 x 7 tablets.
Valam-H tablet 10/160/25 mg	:	Pack of 4 x 7 tablets.
Valam-H Plus tablet 10/320/25 mg	:	Pack of 4 x 7 tablets.

ہدایات:
۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

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