ATRUSAR

Tablets

Composition

Atrusar 80/12.5
Each tablet contains Valsartan 80 mg hydrochlorothiazide 12.5 mg
Atrusar 160/12.5
Each tablet contains Valsartan 160 mg hydrochlorothiazide 12.5 mg
Atrusar 160/25
Each tablet contains Valsartan 160 mg hydrochlorothiazide 25 mg

Action

Mechanism of Action
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. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT2 receptor found in many tissues, but AT2 is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT1 receptor than for the AT2 receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT1 receptor about one 200th that of valsartan itself.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because valsartan does not inhibit ACE (kininase II) it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of valsartan on blood pressure.

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

The mechanism of the antihypertensive effect of thiazides is unknown.

Pharmacokinetics
Valsartan: Valsartan peak plasma concentration is reached 2 to 4 hours after dosing. Valsartan shows bi-exponential decay kinetics following intravenous administration, with an average elimination half-life of about 6 hours. Absolute bioavailability for the capsule formulation is about 25% (range 10%-35%). Food decreases the exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (Cmax) by about 50%. AUC and Cmax values of valsartan increase approximately linearly with increasing dose over the clinical dosing range. Valsartan does not accumulate appreciably in plasma following repeated administration.

Hydrochlorothiazide: Thiazide diuretics are eliminated by the kidney, with a terminal half-life of 5-15 hours.
Geriatric: Exposure (measured by AUC) to valsartan is higher by 70% and the half-life is longer by 35% in the elderly than in the young. No dosage adjustment is necessary
Gender: Pharmacokinetics of valsartan does not differ significantly between males and females.
Race: Pharmacokinetic differences due to race have not been studied.
Renal Insufficiency: There is no apparent correlation between renal function (measured by creatinine clearance) and exposure (measured by AUC) to valsartan in patients with different degrees of renal impairment. Consequently, dose adjustment is not required in patients with mild-to-moderate renal dysfunction. No studies have been performed in patients with severe impairment of renal function (creatinine clearance <10 mL/min). Valsartan is not removed from the plasma by hemodialysis. In the case of severe renal disease, exercise care with dosing of valsartan.
In a study of patients with impaired renal function (mean creatinine clearance of 19 mL/min), the half-life of hydrochlorothiazide elimination was lengthened to 21 hours.
Hepatic Insufficiency: On average, patients with mild-to-moderate chronic liver disease have twice the exposure (measured by AUC values) to valsartan of healthy volunteers (matched by age, sex, and weight). In general, no dosage adjustment is needed in patients with mild-to-moderate liver disease. Care should be exercised in patients with liver disease.

Distribution
Valsartan: The steady state volume of distribution of valsartan after intravenous administration is small (17 L), indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (95%), mainly serum albumin.
Hydrochlorothiazide: Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Metabolism
Valsartan: The primary metabolite, accounting for about 9% of dose, is valeryl 4-hydroxy valsartan. The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes.
Hydrochlorothiazide: Is not metabolized.

Excretion
Valsartan: Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). The recovery is mainly as unchanged drug, with only about 20% of dose recovered as metabolites.
Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance).
Hydrochlorothiazide: Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated as unchanged drug within 24 hours. The elimination half-life is between 5.8 and 18.9 hours.

Pharmacodynamics
Valsartan: Valsartan inhibits the pressor effect of angiotensin II infusions. An oral dose of 80 mg inhibits the pressor effect by about 80% at peak with approximately 30% inhibition persisting for 24 hours. 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.

In multiple-dose studies in hypertensive patients with stable renal insufficiency and patients with renovascular hypertension, valsartan had no clinically significant effects on glomerular filtration rate, filtration fraction, creatinine clearance, or renal plasma flow.

In multiple-dose studies in hypertensive patients, valsartan had no notable effects on total cholesterol, fasting triglycerides, fasting serum glucose, or uric acid.

Hydrochlorothiazide: After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

Indications

- Atrusar (valsartan and hydrochlorothiazide) is indicated for the treatment of hypertension.
- Atrusar may be used in patients whose blood pressure is not adequately controlled on monotherapy.
- Atrusar may be used as initial therapy in patients who are likely to need multiple drugs to achieve blood pressure goals.
- The choice of Atrusar as initial therapy for hypertension should be based on an assessment of potential benefits and risks.

Patients with stage 2 hypertension are at a relatively high risk for cardiovascular events (such as strokes, heart attacks, and heart failure), kidney failure, and vision problems, so prompt treatment is clinically relevant. The decision to use a combination as initial therapy should be individualized and should be shaped by considerations such as baseline blood pressure, the target goal and the incremental likelihood of achieving goal with a combination compared to monotherapy. Individual blood pressure goals may vary based upon the patient's risk.

Contraindications

- Hypersensitivity to any of the components (valsartan and hydrochlorothiazide) and to other sulfonamide-derived drugs.
- Pregnancy
- Severe hepatic impairment
- Biliary cirrhosis and cholestasis
- Anuria; severe renal impairment (creatinine clearance < 30 mL/min)
- Refractory Hypokalaemia, hyponatremia, hypercalcemia, and symptomatic hyperuricemia.

Adverse Reactions

Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reactions 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 practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Hypertension

Valsartan and hydrochlorothiazide has been evaluated for safety in more than 5,700 patients, including over 990 treated for over 6 months, and over 370 for over 1 year.
Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The overall incidence of adverse reactions with Valsartan/HCTZ was comparable to placebo.

The overall frequency of adverse reactions was neither dose-related nor related to gender, age, or race. In controlled clinical trials, discontinuation of therapy due to side effects was required in 2.3% of valsartan-hydrochlorothiazide patients and 3.1% of placebo patients. The most common reasons for discontinuation of therapy with Valsartan/HCTZ were headache and dizziness.

The only adverse reaction that occurred in controlled clinical trials in at least 2% of patients treated with Valsartan/HCTZ and at a higher incidence in valsartan-hydrochlorothiazide (n=4372) than placebo (n=262) patients was nasopharyngitis (2.4% vs. 1.9%).

Dose-related orthostatic effects were seen in less than 1% of patients. In individual trials, a dose-related increase in the incidence of dizziness was observed in patients treated with Valsartan/HCTZ. Other adverse reactions that have been reported with valsartan-hydrochlorothiazide (> 0.2% of valsartan-hydrochlorothiazide patients in controlled clinical trials) without regard to causality, are listed below:

Cardiovascular: Palpitations and tachycardia

Ear and Labyrinth: Tinnitus and vertigo

Gastrointestinal: Dyspepsia, diarrhea, flatulence, dry mouth, nausea, abdominal pain, abdominal pain upper, and vomiting

General and Administration Site Conditions: Asthenia, chest pain, fatigue, peripheral edema and pyrexia

Infections and Infestations: Bronchitis, bronchitis acute, influenza, gastroenteritis, sinusitis, upper respiratory tract infection and urinary tract infection

Investigations: Blood urea increased

Musculoskeletal: Arthralgia, back pain, muscle cramps, myalgia, and pain in extremity

Nervous System: Dizziness postural, paresthesia, and somnolence

Psychiatric: Anxiety and insomnia

Renal and Urinary: Pollakiuria

Reproductive System: Erectile dysfunction

Respiratory, Thoracic and Mediastinal: Dyspnea, cough, nasal congestion, pharyngolaryngeal pain and sinus congestion

Skin and Subcutaneous Tissue: Hyperhidrosis and rash

Vascular: Hypotension
Other reported reactions seen less frequently in clinical trials included abnormal vision, anaphylaxis, bronchospasm, constipation, depression, dehydration, decreased libido, dysuria, epistaxis, flushing, gout, increased appetite, muscle weakness, pharyngitis, pruritus, sunburn, syncope, and viral infection.

Initial Therapy - Hypertension
In a clinical study in patients with severe hypertension (diastolic blood pressure ≥ 110 mmHg and systolic blood pressure ≥ 140 mmHg), the overall pattern of adverse reactions reported through six weeks of follow-up was similar in patients treated with Valsartan/HCTZ as initial therapy and in patients treated with valsartan as initial therapy. Comparing the groups treated with Valsartan/HCTZ (force-titrated to 320/25 mg) and valsartan (force-titrated to 320 mg), dizziness was observed in 6% and 2% of patients, respectively. Hypotension was observed in 1% of those patients receiving Valsartan/HCTZ and 0% of patients receiving valsartan. There were no reported cases of syncope in either treatment group. Laboratory changes with Valsartan/HCTZ as initial therapy in patients with severe hypertension were similar to those reported with Valsartan/HCTZ in patients with less severe hypertension.

Valsartan
In trials in which valsartan was compared to an ACE inhibitor with or without placebo, the incidence of dry cough was significantly greater in the ACE inhibitor group (7.9%) than in the groups who

received valsartan (2.6%) or placebo (1.5%). In a 129-patient trial limited to patients who had had dry cough when they had previously received ACE inhibitors, the incidences of cough in patients who received valsartan, hydrochlorothiazide, or lisinopril were 20%, 19%, 69% respectively ($p < 0.001$).

Other reported reactions seen less frequently in clinical trials included chest pain, syncope, anorexia, vomiting, and angioedema.

***Hydrochlorothiazide*:** Other adverse reactions not listed above that have been reported with hydrochlorothiazide, without regard to causality, are listed below:

Body as a Whole: weakness;

Digestive: pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation;

Hematologic: aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia;

Hypersensitivity: purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever,
Respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions;

Metabolic: hyperglycemia, glycosuria, hyperuricemia;

Musculoskeletal: muscle spasm;

Nervous System/Psychiatric: restlessness;

Renal: renal failure, renal dysfunction, interstitial nephritis;

Skin: erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis;

Special Senses: transient blurred vision, xanthopsia.

Clinical Laboratory Test Findings
In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Valsartan/HCTZ.

***Creatinine/Blood Urea Nitrogen (BUN)*:** Minor elevations in creatinine and BUN occurred in 2% and 15% respectively, of patients taking Valsartan/HCTZ and 0.4% and 6% respectively, given placebo in controlled clinical trials.

***Hemoglobin and Hematocrit*:** Greater than 20% decreases in hemoglobin and hematocrit were observed in less than 0.1% of Valsartan/HCTZ patients, compared with 0% in placebo-treated patients.

***Liver Function Tests*:** Occasional elevations (greater than 150%) of liver chemistries occurred in Diovan HCT-treated patients.

***Neutropenia*:** Neutropenia was observed in 0.1% of patients treated with Valsartan/HCTZ and 0.4% of patients treated with placebo.

Post marketing Experience
The following additional adverse reactions have been reported in valsartan or valsartan/hydrochlorothiazide post marketing experience. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity: There are rare reports of angioedema. Some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Valsartan/HCTZ 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

Clinical Laboratory Tests: Hyperkalemia

Dermatologic: Alopecia
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 post-marketing 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 hypophosphataemia have been observed in a few patients on prolonged thiazide therapy. If hypercalcemia occurs, further diagnostic evaluation is necessary.

Warnings and Precautions

Fetal/Neonatal Morbidity and Mortality
Atrusar can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Drugs that act on the renin-angiotensin system can cause fetal and neonatal morbidity and mortality when used in pregnancy. In several dozen published cases, ACE inhibitor use during the second and third trimesters of pregnancy was associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death.

Intrauterine exposure to thiazide diuretics is associated with fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Hypotension in Volume- and/or Salt-Depleted Patients
Excessive reduction of blood pressure was rarely seen (0.7%) in patients with uncomplicated hypertension treated with (valsartan and hydrochlorothiazide) in controlled trials. 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 and hydrochlorothiazide), or the treatment should start under close medical supervision.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to

further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

Impaired Hepatic Function
Hydrochlorothiazide: Thiazide diuretics 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.

Valsartan: As the majority of valsartan is eliminated in the bile, patients with mild-to-moderate hepatic impairment, including patients with biliary obstructive disorders, showed lower valsartan clearance (higher AUCs). Care should be exercised in administering valsartan to these patients.

Hypersensitivity Reaction
Hydrochlorothiazide: 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
Hydrochlorothiazide: Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

Lithium Interaction
Hydrochlorothiazide: Lithium generally should not be given with thiazides.

Serum Electrolytes
Valsartan – Hydrochlorothiazide: In the controlled trials of various doses of the combination of valsartan and hydrochlorothiazide the incidence of hypertensive patients who developed hypokalemia (serum potassium <3.5 mEq/L) was 3.0%; the incidence of hyperkalemia (serum potassium >5.7 mEq/L) was 0.4%.

Hydrochlorothiazide: All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients, dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Impaired Renal Function
Valsartan: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with valsartan.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. In a 4-day trial of valsartan in 12 patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of valsartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Pregnancy
Category D
There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Nursing Mothers
It is not known whether valsartan is excreted in human milk. 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 the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness of (valsartan and hydrochlorothiazide) in pediatric patients have not been established.

Geriatric Use
No overall difference in the efficacy or safety of valsartan was observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out.

Drug Interactions

Valsartan

No clinically significant pharmacokinetic interactions were observed when valsartan was coadministered 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.

Coadministration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.

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

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

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

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

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

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. Closely monitor blood pressure, renal function and electrolytes in patients on Valsartan/HCTZ and other agents that affect the RAS.

Do not co-administer aliskiren with Valsartan/HCTZ in patients with diabetes. Avoid use of aliskiren with Valsartan/HCTZ in patients with renal impairment (GFR < 60 ml/min).

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.

***Lithium* -** Diuretic agents increase the risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with Valsartan/HCTZ. Monitoring of serum lithium concentrations is recommended during concurrent use.

***Nonsteroidal Anti-inflammatory Drugs (NSAIDS and COX-2 selective inhibitors)* -** When Valsartan/HCTZ and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the 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 4-6 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.

Dosage and Administration

The recommended dose of Atrusar is 1 coated tablet per day. When clinically appropriate either 80 mg valsartan and 12.5 mg hydrochlorothiazide or 160 mg valsartan and 12.5 mg hydrochlorothiazide may be used, when necessary 160 mg valsartan and 25 mg hydrochlorothiazide. The maximum antihypertensive effect is seen within 2 to 4 weeks.

Renal impairment

No dosage adjustment is required for patients with mild to moderate renal impairment (Glomerular Filtration Rate (GFR) ≥30 mL/min). Due to the hydrochlorothiazide component, Atrusar is contraindicated in patients with anuria and should be used with caution in patients with severe renal impairment (GFR <30 mL/min). Thiazide diuretics are ineffective as monotherapy in severe renal impairment (GFR <30 mL/min) but may be useful in these patients, when used with due caution in combination with a loop diuretic even in patients with GFR <30 mL/min.

Hepatic impairment

No dosage adjustment is required in patients with mild to moderate hepatic impairment. Due to the hydrochlorothiazide component, Atrusar should be used with particular caution in patients with severe hepatic impairment. Due to the valsartan component, Atrusar should be used with particular caution in patients with biliary obstructive disorders.

Paediatrics (below 18 years)

The safety and efficacy of Atrusar have not been established in children below the age of 18 years.

Overdosage

Valsartan – Hydrochlorothiazide

Limited data are available related to overdosage in humans. The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. Depressed level of consciousness, circulatory collapse and shock have been reported. If symptomatic hypotension should occur, supportive treatment should be instituted.

Valsartan is not removed from the plasma by dialysis.

The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The most common signs and symptoms observed in patients are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

In rats and marmosets, single oral doses of valsartan up to 1524 and 762 mg/kg in combination with hydrochlorothiazide at doses up to 476 and 238 mg/kg, respectively, were very well tolerated without any treatment-related effects. These no adverse effect doses in rats and marmosets, respectively, represent 46.5 and 23 times the maximum recommended human dose (MRHD) of valsartan and 188 and 113 times the MRHD of hydrochlorothiazide on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient.)

Valsartan

Valsartan was without grossly observable adverse effects at single oral doses up to 2000 mg/kg in rats and up to 1000 mg/kg in marmosets, except for salivation and diarrhea in the rat and vomiting in the

marmoset at the highest dose (60 and 31 times, respectively, the maximum recommended human dose on a mg/m² basis). (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

Hydrochlorothiazide
The oral LD50 of hydrochlorothiazide is greater than 10 g/kg in both mice and rats, which represents 2027 and 4054 times, respectively, the maximum recommended human dose on a mg/m² basis. (Calculations assume an oral dose of 25 mg/day and a 60-kg patient.)

Storage Instructions
Store at. 25°C. Protect from moisture.

Presentation
Atrusar80/12.5
Box of 28
Atrusar160/12.5
Box of 30
Atrusar160/25
Box of 30