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

AVOID USE IN PREGNANCY
When pregnancy is detected, discontinue as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus.

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

Adverse drug reactions reported in clinical trials and laboratory findings occurring more frequently with valsartan plus hydrochlorothiazide versus placebo and individual post-marketing reports are presented below according to system organ class. Adverse reactions known to occur with each component given individually but which have not been seen in clinical trials may occur during treatment with valsartan/hydrochlorothiazide.

Adverse drug reactions are ranked by frequency, the most frequent first, using the following convention: very common (> 1/10); common (> 1/100 to < 1/10); uncommon (> 1/1,000 to < 1/100); rare (> 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Frequency of adverse drug reactions with valsartan/hydrochlorothiazide

Metabolism and nutrition disorders

Uncommon	Dehydration

Nervous system disorders

Very rare	Dizziness
Uncommon	Paraesthesia
Not known	Syncope

Eye disorders
Uncommon Vision blurred
Ear and labyrinth disorders
Uncommon Tinnitus
Vascular disorders
Uncommon Hypotension
Respiratory, thoracic and mediastinal disorders
Uncommon Cough
Not known Non cardiogenic pulmonary edema
Gastrointestinal disorders
Very rare Diarrhea
Musculoskeletal and connective tissue disorders
Uncommon Myalgia
Very rare Arthralgia
Renal and urinary disorders
Not known impaired renal function
General disorders and administration site conditions
Uncommon Fatigue
Investigations
Not known Serum uric acid increased, Serum bilirubin and Serum creatinine Increased, Hypokalemia, Hyponatremia, Elevation of Blood Urea Nitrogen, Neutropenia.

The following events have also been observed during clinical trials in hypertensive patients irrespective of their causal association with the study drug: Abdominal pain, abdominal pain upper, anxiety, arthritis, asthenia, back pain, bronchitis, bronchitis acute, chest pain, dizziness postural dyspepsia, dyspnea, dry mouth, epistaxis, erectile dysfunction, gastroenteritis, headache hyperhydrosis, hypoesthesia, influenza, insomnia, ligament sprain, muscle spasms, muscle strain, nasal congestion, nasopharyngitis, nausea, neck pain, edema, edema peripheral, otitis media, pain in extremity, palpitations, pharyngolaryngal pain, pollakiuria, pyrexia, sinusitis, sinus congestion, somnolence, tachycardia, upper respiratory tract infections, urinary tract infections, vertigo, viral infections, vision disturbance.

Additional information on the individual components
Adverse reactions previously reported with one of the individual components may be potential undesirable effects with Valsartan/HCTZ as well, even if not observed in clinical trials or during post-marketing period.
Blood and lymphatic system disorders
Not known Decrease in hemoglobin, decrease in hematocrit, thrombocytopenia
Immune system disorders
Not known other hypersensitivity/allergic reactions including serum sickness
Metabolism and nutrition disorders
Not known Increase of serum potassium
Ear and labyrinth disorders
Uncommon Vertigo
Vascular disorders
Not known Vasculitis
Gastrointestinal disorders
Uncommon Abdominal pain
Hepatobiliary disorders
Not known Elevation of liver function values
Skin and subcutaneous tissue disorders
Not known Angioedema, rash, pruritus
Renal and urinary disorders
Not known renal failure

The following events have also been observed during clinical trials in hypertensive patients irrespective of their causal association with the study drug: Arthralgia, asthenia, back pain, diarrhea,

dizziness, headache, insomnia, libido decrease, nausea, edema, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, viral infections.

Frequency of adverse reactions with Hydrochlorothiazide

Metabolism and nutrition disorders

Very common: mainly at higher doses, blood lipids increased.

Common: hypomagnesemia, and hyperuricemia.

Rare: hypercalcemia, hyperglycemia, glycosuria and worsening of diabetic metabolic state.

Very rare: hypochloremic alkalosis.

Skin and subcutaneous tissue disorders

Common: urticaria and other forms of rash.

Rare: photosensitivity reaction.

Very rare: necrotizing vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus.

Not known erythema multiforme

Gastrointestinal disorders

Common: decreased appetite, mild nausea and vomiting.

Rare: abdominal discomfort, constipation and diarrhea.

Very rare: pancreatitis.

Hepatobiliary disorders

Rare: cholestasis or jaundice.

Vascular disorders

Common: orthostatic hypotension, which may be aggravated by alcohol, anesthetics or sedatives.

Cardiac disorders

Rare: arrhythmias.

Nervous system disorders

Rare: Headaches, dizziness, sleep disorders, depression and paresthesia

Eye disorders

Rare: Visual impairment particularly in the first few weeks of treatment.

Not known: acute angle-closure glaucoma

Blood and lymphatic system disorders

Rare: thrombocytopenia sometimes with purpura.

Very rare: leucopenia, agranulocytosis, bone marrow failure and hemolytic anaemia.

Not known: aplastic anemia

Reproductive system and breast disorders

Common: impotence.

Immune system disorders

Very rare: hypersensitivity reactions - respiratory distress including pneumonitis and pulmonary edema.

Renal and urinary disorders

Not known: acute renal failure, renal disorder

General disorders and administration site conditions

Not known pyrexia, asthenia

Musculoskeletal and connective tissue disorders

Not known muscle spasms

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
(Valsartan and hydrochlorothiazide), like other drugs that act on the renin angiotensin system, can cause fetal and neonatal morbidity and death when used during the second or third trimester of

pregnancy. (Valsartan and hydrochlorothiazide) 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.

Angiotensin II receptor antagonists, like valsartan, and angiotensin converting enzyme (ACE) inhibitors exert similar effects on the renin-angiotensin system. 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. Oligohydramnios was also reported, presumably from decreased fetal renal function.

Oligohydramnios was associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus were also reported, although it is not clear whether these occurrences were due to exposure to the drug.

When pregnancy occurs in a patient using (valsartan and hydrochlorothiazide) the physician should discontinue valsartan treatment as soon as possible. The physician should inform the patient about potential risks to the fetus based on the time of gestational exposure to (valsartan and hydrochlorothiazide) (first trimester only or later). If exposure occurs beyond the first trimester, an ultrasound examination should be done.

In rare cases when another antihypertensive agent cannot be used to treat the pregnant patient, serial ultrasound examinations should be performed to assess the intraamniotic environment. Routine fetal testing with non-stress tests, biophysical profiles, and/or contraction stress tests may be appropriate based on gestational age and standards of care in the community. If oligohydramnios occurs in these situations, individualized decisions about continuing or discontinuing (valsartan and hydrochlorothiazide) treatment and about pregnancy management should be made by the patient, her physician, and experts in the management of high risk pregnancy. Patients and physicians should be aware that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to (valsartan and hydrochlorothiazide) should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, these infants may require blood pressure and renal perfusion support. Exchange transfusion or dialysis may be required to reverse hypotension and/or support decreased renal function.

Healthcare professionals who prescribe drugs acting directly on the renin angiotensin system should counsel women of childbearing potential about the risks of these agents during pregnancy.

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: The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes. The inhibitory or induction potential of valsartan on CYP 450 is also unknown.

Hydrochlorothiazide
When administered concurrently, the following drugs may interact with thiazide diuretics:
Alcohol, Barbiturates, or Narcotics - Potentiation of orthostatic hypotension may occur.
Antidiabetic Drugs (oral agents and insulin) - Dosage adjustment of the antidiabetic drug may be required.
Other Antihypertensive Drugs - Additive effect or potentiation.
Cholestyramine and Colestipol Resins - Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43% respectively.
Corticosteroids, ACTH - Intensified electrolyte depletion, particularly hypokalemia.
Pressor Amines (e.g., norepinephrine) - Possible decreased response to pressor amines but not sufficient to preclude their use.
Skeletal Muscle Relaxants, Nondepolarizing (e.g., tubocurarine) - Possible increased responsiveness to the muscle relaxant.
Lithium - Should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.
Nonsteroidal Anti-inflammatory Drugs - In some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when (valsartan and hydrochlorothiazide) 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.

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

Overdose with valsartan may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock. If the ingestion is recent, a sufficient amount of activated charcoal should be administered. Otherwise, the usual treatment would be intravenous infusion of normal saline solution.

Valsartan cannot be eliminated by means of haemodialysis because it is strongly bound to plasma proteins. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

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