

For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

VALZAAR
(Valsartan Tablets I.P.)

COMPOSITION

VALZAAR - 40

Each film coated tablet contains:

Valsartan I.P. 40 mg

Colors: Yellow Oxide of Iron, Red Oxide of Iron and Titanium Dioxide I.P.

VALZAAR -80

Each film coated tablet contains:

Valsartan I.P. 80 mg

Colors: Red Oxide of Iron and Titanium Dioxide I.P.

VALZAAR -160

Each film coated tablet contains:

Valsartan I.P. 160 mg

Colors: Red Oxide of Iron and Titanium Dioxide I.P.

WARNING: FETAL TOXICITY

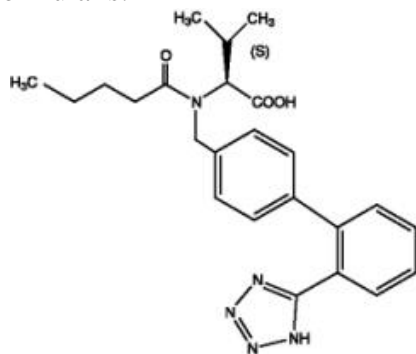
When pregnancy is detected, discontinue product as soon as possible

Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

DESCRIPTION

Valsartan is a nonpeptide, orally active, and specific angiotensin II receptor blocker acting on the AT₁ receptor subtype.

Valsartan is chemically described as N-(1-oxopentyl)-N-[[2'-(1H-tetrazol-5-yl) [1,1'-biphenyl]-4-yl]methyl]-L-valine. Its empirical formula is C₂₄H₂₉N₅O₃, its molecular weight is 435.5, and its structural formula is:



Valsartan is a white to practically white fine powder. It is soluble in ethanol and methanol and slightly soluble in water.

INDICATIONS AND USAGE

Hypertension

Valsartan 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. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including the class to which valsartan principally belongs. There are no controlled trials in hypertensive patients demonstrating risk reduction with valsartan.

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 one drug to achieve blood pressure goals.

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (e.g., patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

Valsartan may be used alone or in combination with other antihypertensive agents.

Heart Failure

Valsartan is indicated for the treatment of heart failure (NYHA class II-IV). In a controlled clinical trial, valsartan significantly reduced hospitalizations for heart failure. There is no evidence that valsartan provides added benefits when it is used with an adequate dose of an ACE inhibitor.

Post-Myocardial Infarction

In clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction, Valsartan is indicated to reduce cardiovascular mortality.

DOSAGE AND ADMINISTRATION

Adult Hypertension

The recommended starting dose of valsartan is 80 mg or 160 mg once daily when used as monotherapy in patients who are not volume-depleted. Patients requiring greater reductions may be started at the higher dose. Valsartan may be used over a dose range of 80 mg to 320 mg daily, administered once a day.

The antihypertensive effect is substantially present within 2 weeks and maximal reduction is generally attained after 4 weeks. If additional antihypertensive effect is required over the starting dose range, the dose may be increased to a maximum of 320 mg or a diuretic may be added. Addition of a diuretic has a greater effect than dose increases beyond 80 mg.

No initial dosage adjustment is required for elderly patients, for patients with mild or moderate renal impairment, or for patients with mild or moderate liver insufficiency. Care should be exercised with dosing of valsartan in patients with hepatic or severe renal impairment.

Valsartan may be administered with other antihypertensive agents.

Valsartan may be administered with or without food.

Pediatric Hypertension 6 to 16 Years of Age

For children who can swallow tablets, the usual recommended starting dose is 1.3 mg/kg once daily (up to 40 mg total). The dosage should be adjusted according to blood pressure response. Doses higher than 2.7 mg/kg (up to 160 mg) once daily have not been studied in pediatric patients 6 to 16 years old.

For children who cannot swallow tablets, or children for whom the calculated dosage (mg/kg) does not correspond to the available tablet strengths of valsartan, the use of a suspension is recommended. Follow the suspension preparation instructions below to administer valsartan as a suspension. When the suspension is replaced by a tablet, the dose of valsartan may have to be increased. The exposure to valsartan with the suspension is 1.6 times greater than with the tablet.

No data are available in pediatric patients either undergoing dialysis or with a glomerular filtration rate <30 mL/min/1.73 m².

Valsartan is not recommended for patients <6 years old.

Heart Failure

The recommended starting dose of valsartan is 40 mg twice daily. Uptitration to 80 mg and 160 mg twice daily should be done to the highest dose, as tolerated by the patient. Consideration should be given to reducing the dose of concomitant diuretics. The maximum daily dose administered in clinical trials is 320 mg in divided doses.

Post-Myocardial Infarction

Valsartan may be initiated as early as 12 hours after a myocardial infarction. The recommended starting dose of valsartan is 20 mg twice daily. Patients may be uptitrated within 7 days to 40 mg twice daily, with subsequent titrations to a target maintenance dose of 160 mg twice daily, as tolerated by the patient. If symptomatic hypotension or renal dysfunction occurs, consideration should be given to a dosage reduction. Valsartan may be given with other standard post-myocardial infarction treatment, including thrombolytics, aspirin, beta-blockers, and statins.

CONTRAINDICATIONS

Do not use in patients with known hypersensitivity to any component.

Do not coadminister aliskiren with valsartan in patients with diabetes.

WARNINGS AND 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 Valsartan as soon as possible.

Hypotension

Excessive hypotension was rarely seen (0.1%) in patients with uncomplicated hypertension treated with Valsartan alone. 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, or the treatment should start under close medical supervision.

Caution should be observed when initiating therapy in patients with heart failure or post-myocardial infarction patients. Patients with heart failure or post-myocardial infarction patients given Valsartan commonly have some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed. In controlled trials in heart failure patients, the incidence of hypotension in valsartan-treated patients was 5.5% compared to 1.8% in placebo-treated patients. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), hypotension in post-myocardial infarction patients led to permanent discontinuation of therapy in 1.4% of valsartan-treated patients and 0.8% of captopril-treated patients.

If excessive 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 Renal Function

Changes in renal function including acute renal failure can be caused by drugs that inhibit the renin-angiotensin system and by diuretics. Patients whose renal function may depend in part on

the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing acute renal failure on valsartan. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on valsartan.

Hyperkalemia

Some patients with heart failure have developed increases in potassium. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of valsartan may be required.

ADVERSE REACTIONS

Clinical Studies Experience

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 practice.

Adult Hypertension

Valsartan has been evaluated for safety in more than 4,000 patients, including over 400 treated for over 6 months, and more than 160 for over 1 year. Adverse reactions have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The overall incidence of adverse reactions with valsartan was similar to placebo.

The overall frequency of adverse reactions was neither dose-related nor related to gender, age, race, or regimen. Discontinuation of therapy due to side effects was required in 2.3% of valsartan patients and 2.0% of placebo patients. The most common reasons for discontinuation of therapy with valsartan were headache and dizziness.

The adverse reactions that occurred in placebo-controlled clinical trials in at least 1% of patients treated with Valsartan and at a higher incidence in valsartan (n=2,316) than placebo (n=888) patients included viral infection (3% vs. 2%), fatigue (2% vs. 1%), and abdominal pain (2% vs. 1%).

Headache, dizziness, upper respiratory infection, cough, diarrhea, rhinitis, sinusitis, nausea, pharyngitis, edema, and arthralgia occurred at a more than 1% rate but at about the same incidence in placebo and valsartan patients.

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, HCTZ, or lisinopril were 20%, 19%, and 69% respectively (p <0.001).

Dose-related orthostatic effects were seen in less than 1% of patients. An increase in the incidence of dizziness was observed in patients treated with valsartan 320 mg (8%) compared to 10 to 160 mg (2% to 4%).

Valsartan has been used concomitantly with hydrochlorothiazide without evidence of clinically important adverse interactions.

Other adverse reactions that occurred in controlled clinical trials of patients treated with valsartan (>0.2% of valsartan patients) are listed below. It cannot be determined whether these events were causally related to valsartan.

Body as a Whole: Allergic reaction and asthenia

Cardiovascular: Palpitations

Dermatologic: Pruritus and rash

Digestive: Constipation, dry mouth, dyspepsia, and flatulence

Musculoskeletal: Back pain, muscle cramps, and myalgia

Neurologic and Psychiatric: Anxiety, insomnia, paresthesia, and somnolence

Respiratory: Dyspnea

Special Senses: Vertigo

Urogenital: Impotence

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

Pediatric Hypertension

Valsartan has been evaluated for safety in over 400 pediatric patients aged 6 to 17 years and more than 160 pediatric patients aged 6 months to 5 years. No relevant differences were identified between the adverse experience profile for pediatric patients aged 6 to 16 years and that previously reported for adult patients. Headache and hyperkalemia were the most common adverse events suspected to be study drug-related in older children (6 to 17 years old) and younger children (6 months to 5 years old), respectively. Hyperkalemia was mainly observed in children with underlying renal disease. Neurocognitive and developmental assessment of pediatric patients aged 6 to 16 years revealed no overall clinically relevant adverse impact after treatment with valsartan for up to 1 year.

Valsartan is not recommended for pediatric patients under 6 years of age. In a study (n=90) of pediatric patients (1 to 5 years), two deaths and three cases of on-treatment transaminase elevations were seen in the one-year open-label extension phase. These 5 events occurred in a study population in which patients frequently had significant co-morbidities. A causal relationship to valsartan has not been established. In a second study in which 75 children aged 1 to 6 years were randomized, no deaths and one case of marked liver transaminase elevations occurred during a 1 year open-label extension.

Heart Failure

The adverse experience profile of valsartan in heart failure patients was consistent with the pharmacology of the drug and the health status of the patients. In the valsartan Heart Failure

Trial, comparing valsartan in total daily doses up to 320 mg (n=2,506) to placebo (n=2,494), 10% of valsartan patients discontinued for adverse reactions vs. 7% of placebo patients.

The table shows adverse reactions in double-blind short-term heart failure trials, including the first 4 months of the Valsartan Heart Failure Trial, with an incidence of at least 2% that were more frequent in valsartan-treated patients than in placebo-treated patients. All patients received standard drug therapy for heart failure, frequently as multiple medications, which could include diuretics, digitalis, beta-blockers. About 93% of patients received concomitant ACE inhibitors.

	Valsartan (n=3,282)	Placebo (n=2,740)
Dizziness	17%	9%
Hypotension	7%	2%
Diarrhea	5%	4%
Arthralgia	3%	2%
Fatigue	3%	2%
Back Pain	3%	2%
Dizziness, postural	2%	1%
Hyperkalemia	2%	1%
Hypotension, postural	2%	1%

Discontinuations occurred in 0.5% of valsartan-treated patients and 0.1% of placebo patients for each of the following: elevations in creatinine and elevations in potassium.

Other adverse reactions with an incidence greater than 1% and greater than placebo included headache NOS, nausea, renal impairment NOS, syncope, blurred vision, upper abdominal pain and vertigo. (NOS = not otherwise specified).

From the long-term data in the Valsartan Heart Failure Trial, there did not appear to be any significant adverse reactions not previously identified.

Post-Myocardial Infarction

The safety profile of valsartan was consistent with the pharmacology of the drug and the background diseases, cardiovascular risk factors, and clinical course of patients treated in the post-myocardial infarction setting. The table shows the percentage of patients discontinued in the valsartan and captopril-treated groups in the Valsartan in Acute Myocardial Infarction Trial (VALIANT) with a rate of at least 0.5% in either of the treatment groups.

Discontinuations due to renal dysfunction occurred in 1.1% of valsartan-treated patients and 0.8% of captopril-treated patients.

	Valsartan (n=4,885)	Captopril (n=4,879)
Discontinuation for adverse reaction	5.8%	7.7%
Adverse reactions		
Hypotension NOS	1.4%	0.8%
Cough	0.6%	2.5%

Blood creatinine increased	0.6%	0.4%
Rash NOS	0.2%	0.6%

Postmarketing Experience

The following additional adverse reactions have been reported in postmarketing experience:

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

Blood and Lymphatic: There are very rare reports of thrombocytopenia

Vascular: Vasculitis

Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

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.

DRUG INTERACTIONS

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 coadministered 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. Coadministration of inhibitors of the uptake transporter (rifampin, cyclosporine) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.

Potassium: Concomitant use of valsartan with other agents that block the renin-angiotensin system, potassium sparing diuretics (e.g. spironolactone, triamterene, 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.

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.

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 valsartan and other agents that affect the RAS.

Do not coadminister aliskiren with valsartan in patients with diabetes. Avoid use of aliskiren with Valsartan in patients with renal impairment (GFR <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, including valsartan. Monitor serum lithium levels during concomitant use.

Clinical Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of valsartan.

Creatinine: Minor elevations in creatinine occurred in 0.8% of patients taking valsartan and 0.6% given placebo in controlled clinical trials of hypertensive patients. In heart failure trials, greater than 50% increases in creatinine were observed in 3.9% of valsartan-treated patients compared to 0.9% of placebo-treated patients. In post-myocardial infarction patients, doubling of serum creatinine was observed in 4.2% of valsartan-treated patients and 3.4% of captopril-treated patients.

Hemoglobin and Hematocrit: Greater than 20% decreases in hemoglobin and hematocrit were observed in 0.4% and 0.8%, respectively, of valsartan patients, compared with 0.1% and 0.1% in placebo-treated patients. One valsartan patient discontinued treatment for microcytic anemia.

Liver Function Tests: Occasional elevations (greater than 150%) of liver chemistries occurred in valsartan-treated patients. Three patients (< 0.1%) treated with valsartan discontinued treatment for elevated liver chemistries.

Neutropenia: Neutropenia was observed in 1.9% of patients treated with valsartan and 0.8% of patients treated with placebo.

Serum Potassium: In hypertensive patients, greater than 20% increases in serum potassium were observed in 4.4% of valsartan-treated patients compared to 2.9% of placebo-treated patients. In heart failure patients, greater than 20% increases in serum potassium were observed in 10.0% of valsartan-treated patients compared to 5.1% of placebo-treated patients.

Blood Urea Nitrogen (BUN): In heart failure trials, greater than 50% increases in BUN were observed in 16.6% of valsartan-treated patients compared to 6.3% of placebo-treated patients.

USE IN SPECIFIC POPULATIONS

Pregnancy

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 valsartan as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimesters of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, 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 valsartan, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to valsartan for hypotension, oliguria, and hyperkalemia.

Nursing Mothers

It is not known whether valsartan is excreted in human milk. Valsartan was excreted in the milk of lactating rats; however, animal breast milk drug levels may not accurately reflect human breast milk levels. Because many drugs are excreted into human milk and because of the potential for adverse reactions in nursing infants from valsartan, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The antihypertensive effects of valsartan have been evaluated in two randomized, double-blind clinical studies in pediatric patients from 1-5 and 6-16 years of age. The pharmacokinetics of valsartan have been evaluated in pediatric patients 1 to 16 years of age. Valsartan was generally well tolerated in children 6-16 years and the adverse experience profile was similar to that described for adults.

In children and adolescents with hypertension where underlying renal abnormalities may be more common, renal function and serum potassium should be closely monitored as clinically indicated.

Valsartan is not recommended for pediatric patients under 6 years of age due to safety findings for which a relationship to treatment could not be excluded.

No data are available in pediatric patients either undergoing dialysis or with a glomerular filtration rate <30 mL/min/1.73 m².

There is limited clinical experience with valsartan in pediatric patients with mild to moderate hepatic impairment.

Daily oral dosing of neonatal/juvenile rats with valsartan at doses as low as 1 mg/kg/day (about 10% of the maximum recommended pediatric dose on a mg/m² basis) from postnatal day 7 to postnatal day 70 produced persistent, irreversible kidney damage. These kidney effects in neonatal rats represent expected exaggerated pharmacological effects that are observed if rats are treated during the first 13 days of life. Since this period coincides with up to 44 weeks after conception in humans, it is not considered to point toward an increased safety concern in 6 to 16 year old children.

Neonates with a history of in utero exposure to valsartan:

If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

Geriatric Use

In the controlled clinical trials of valsartan, 1,214 (36.2%) hypertensive patients treated with valsartan were ≥ 65 years and 265 (7.9%) were ≥ 75 years. 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.

Of the 2,511 patients with heart failure randomized to valsartan in the Valsartan Heart Failure Trial, 45% (1,141) were 65 years of age or older. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), 53% (2,596) of the 4,909 patients treated with valsartan and 51% (2,515) of the 4,885 patients treated with valsartan + captopril were 65 years of age or older. There were no notable differences in efficacy or safety between older and younger patients in either trial.

Renal Impairment

Safety and effectiveness of valsartan in patients with severe renal impairment (CrCl \leq 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

No dose adjustment is necessary for patients with mild-to-moderate liver disease. No dosing recommendations can be provided for patients with severe liver disease.

OVERDOSAGE

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 hemodialysis.

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.)

CLINICAL PHARMACOLOGY

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 AT₂receptor 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 increased plasma levels of angiotensin II following AT₁ receptor blockade with valsartan may stimulate the unblocked 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.

Pharmacodynamics

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.

Pharmacokinetics

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 valsartan is about 25% (range 10% to 35%). The bioavailability of the suspension is 1.6 times greater than with the tablet. With the tablet, food decreases the exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%. AUC and C_{max} values of valsartan increase approximately linearly with increasing dose over the clinical dosing range. Valsartan does not accumulate appreciably in plasma following repeated administration.

Metabolism and Elimination:

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. The primary metabolite, accounting for about 9% of dose, is valeryl 4-hydroxy valsartan. In vitro metabolism studies involving recombinant CYP 450 enzymes indicated that the CYP 2C9 isoenzyme is responsible for the formation of valeryl-4-hydroxy valsartan. Valsartan does not inhibit CYP 450 isozymes at clinically relevant concentrations. CYP 450 mediated drug interaction between valsartan and coadministered drugs are unlikely because of the low extent of metabolism.

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).

Distribution:

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.

Special Populations:

Pediatric: In a study of pediatric hypertensive patients (n=26, 1 to 16 years of age) given single doses of a suspension of valsartan (mean: 0.9 to 2 mg/kg), the clearance (L/h/kg) of valsartan for children was similar to that of adults receiving the same formulation.

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.

Heart Failure: The average time to peak concentration and elimination half-life of valsartan in heart failure patients are similar to those observed in healthy volunteers. AUC and C_{max} values of valsartan increase linearly and are almost proportional with increasing dose over the clinical dosing range (40 to 160 mg twice a day). The average accumulation factor is about 1.7. The apparent clearance of valsartan following oral administration is approximately 4.5 L/h. Age does not affect the apparent clearance in heart failure patients.

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.

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.

NONCLINICAL TOXICOLOGY**Carcinogenesis, Mutagenesis, Impairment of Fertility**

There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for up to 2 years at doses up to 160 and 200 mg/kg/day, respectively. These doses in mice and rats are about 2.6 and 6 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.)

Mutagenicity assays did not reveal any valsartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with Salmonella (Ames)

and E coli; a gene mutation test with Chinese hamster V79 cells; a cytogenetic test with Chinese hamster ovary cells; and a rat micronucleus test.

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 times the maximum recommended human dose on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

No teratogenic effects were observed when valsartan was administered to pregnant mice and rats at oral doses up to 600 mg/kg/day and to pregnant rabbits at oral doses up to 10 mg/kg/day. However, significant decreases in fetal weight, pup birth weight, pup survival rate, and slight delays in developmental milestones were observed in studies in which parental rats were treated with valsartan at oral, maternally toxic (reduction in body weight gain and food consumption) doses of 600 mg/kg/day during organogenesis or late gestation and lactation. In rabbits, fetotoxicity (i.e., resorptions, litter loss, abortions, and low body weight) associated with maternal toxicity (mortality) was observed at doses of 5 and 10 mg/kg/day. The no observed adverse effect doses of 600, 200, and 2 mg/kg/day in mice, rats and rabbits represent 9, 6, and 0.1 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.

EXPIRY DATE

Do not use after the date of expiry.

STORAGE

Store at a temperature not exceeding 25°C, protected from light and moisture.
Keep all medicines out of the reach of children.

PRESENTATION

Valzaar- 40, Valzaar- 80 & Valzaar-160 are available in blister pack of 10 tablets.

MARKETED BY



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