Valid™
[VALSARTAN]

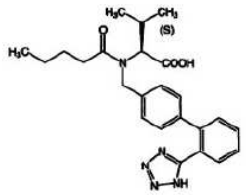
ویلڈ
(والسارٹان)

COMPOSITION:
Valid 80mg
Each film coated tablet contains valsartan 80mg. .....USP
Valid 160mg
Each film coated tablet contains valsartan 160mg .... USP

DRUG 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 $C_{24}H_{29}N_5O_3$, 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.

Valsartan is available as tablets for oral administration containing 80 mg, 160 mg of valsartan.

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 re-absorption 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 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.

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%-35%). The bioavailability of the suspension (see DOSAGE AND ADMINISTRATION; Pediatric Hypertension) 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 (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.

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. The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes.

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, 1-16 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 [see DOSAGE AND ADMINISTRATION].

Gander: 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 that observed in healthy volunteers. AUC and Cmax 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 [see DOSAGE AND ADMINISTRATION].

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 [see DOSAGE AND ADMINISTRATION].

INDICATIONS:
Hypertension

Valsartan is indicated for the treatment of hypertension. It 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 :
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.

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 closes.

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.

SIDE EFFECTS:

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.

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.

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%).

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.

Heart Failure

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, or 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%

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 percent 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.

	Valsartan (n=4,885)	Captopril (n=4,879)
Discontinuation for adverse reaction	5.8%	7.7%
Adverse reactions		
Hypotension NOS	1.4%	0.5%
Cough	0.6%	2.5%
Blood creatinine increased	0.6%	0.4%
Rash NOS	0.2%	0.6%

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

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.

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.

As with other drugs that block angiotensin II or its effects, concomitant use of 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.

WARNINGS:

ncluded as a part of the PRECAUTIONS section.

PRECAUTIONS:

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.

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.

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 Hepatic Function

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.

Impaired Renal Function

In studies of ACE inhibitors in hypertensive 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 hypertensive 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.

OVERDOSE:

Limited data is 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 levels 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).

CONTRAINDICATIONS:

None

HOW SUPPLIED / STORAGE AND HANDLING:

Valic (valsartan) tablets 80mg and 160mg are available in blister packs of 14 tablets.

Store below 30°C.
Protect from light, heat and moisture.
Use as directed by registered physician.
Keep all medicine out of reach of children.

ہدایات:
صرف رجسٹرڈ ڈاکٹر کے نسخہ پر ہی فروخت کی جائے۔
گرمی، روشنی اور نمی سے محفوظ رکھیں۔ ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔

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