Use upon doctor's instruction only 8030238-8883

VALZAAR

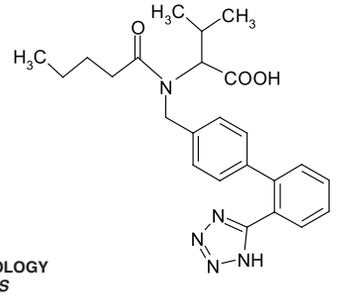
(Valsartan Capsules, 40 mg, 80 mg & 160 mg)

COMPOSITION

VALZAAR 40: Each hard gelatin capsule contains Valsartan..... 40mg
VALZAAR 80: Each hard gelatin capsule contains Valsartan..... 80mg
VALZAAR 160: Each hard gelatin capsule contains Valsartan...160mg

PROPERTIES

Valsartan is a nonpeptide Angiotensin II receptor antagonist and act competitively at, and is selective for, angiotensin II AT_1 receptor subtype, which is responsible for most of the known effects of Angiotensin II. It is white to off white powder, very soluble in methanol and in ethanol; sparingly soluble in ethyl acetate; slightly soluble in chloroform; practically insoluble in water. It 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 $C_{24}H_{29}N_5O_3$ with a molecular weight of 435.5, and its structural formula is:



CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

The peptide hormone Angiotensin II, the primary effector of the renin-angiotensin cascade, stimulates many physiological systems including those involved in blood pressure regulation and renal function; importantly it has potent pressor activity. On this basis ACE inhibition and Angiotensin II antagonism have established a role in the treatment of hypertension.

Two primary subtypes of Angiotensin II receptor have been identified: AT_1 and AT_2. AT_1 receptors predominate and are responsible for most known actions of Angiotensin including vasoconstriction, aldosterone release and vascular hypertrophy.

Valsartan displaces Angiotensin II from AT_1 receptors and thus antagonizing these effects. It produces persistent blood pressure reductions in patients with mild to moderate hypertension. In comparison to other antihypertensive drugs valsartan therapy leads to similar blood pressure reductions, while exhibiting a favourable tolerability profile. Blockade of 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. 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

Absorption

The drug is rapidly absorbed with a peak plasma concentration (C_{max}) of 1.64 mg/L and the peak plasma concentration being achieved 2 to 4 hours after dosing. The absolute bioavailability for the capsule formulation is 25% (range 10%-35%). 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.

Distribution

Volume of distribution at steady state was estimated to be 17 L. Valsartan was extensively (96%) bound to human serum proteins in an in vitro equilibrium dialysis study using [^{14}C] valsartan 0.05 to 5 mg/L. This value was consistent with the 85 to 99% plasma protein binding rate reported in patients (presumably with hypertension) during 8 week's treatment with valsartan 10 to 160 mg/day.

Metabolism

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.

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. 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). The elimination half-life for valsartan was found to be 6.1 hours.

INDICATIONS

VALZAAR is indicated for the treatment of mild to moderate hypertension and heart failure.

CONTRAINDICATIONS

VALZAAR is contraindicated in patients who are hypersensitive to Angiotensin II receptor blockers.

WARNINGS

Hypotension in Volume and/or Salt-Depleted Patients: Excessive reduction of blood pressure was rarely seen (0.1%) in patients with uncomplicated hypertension. 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 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.

PRECAUTIONS

HEPATIC INSUFFICIENCY: 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.

RENAL INSUFFICIENCY: 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 have been associated with oliguria and/ or progressive azotemia and (rarely) with acute renal failure and/or death. Valsartan would be expected to behave similarly.

Use In Pregnancy, Nursing Mothers And Children

PREGNANT WOMEN: Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. When pregnancy is detected, valsartan should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NURSING MOTHERS: It is not known whether valsartan is excreted in human milk, but valsartan was excreted in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

CHILDREN: Safety and effectiveness in pediatric patients have not been established.

SIDE EFFECTS

Adverse experiences have generally been mild and transient in nature. The most common side effects (2.3%) with valsartan are headache and dizziness. Other side effects are viral infection (3%), fatigue (2%), and abdominal pain (2%).

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%).

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%).

Greater than 20% increases in serum potassium were observed in 4.4% of valsartan-treated patients compared to 2.9% of placebo-treated patients. No patient treated with valsartan discontinued therapy for hyperkalemia.

INFORM YOUR DOCTOR IN CASE OF ANY ADVERSE REACTIONS RELATED TO DRUG USE

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.

DOSAGE AND ADMINISTRATION

For hypertension, the recommended starting dose of VALZAAR is 80 mg once daily taken with or without food, when used as monotherapy in patients who are not volume-depleted. VALZAAR may be used over a dose range of 80 mg to 320 mg daily, administered once-a-day.

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.

VALZAAR may be administered with other antihypertensive agents.

For heart failure, the recommended starting dose of VALZAAR is 40 mg twice daily and the dose should be titrated upto 160 mg twice daily, as tolerated by the patient.

OVERDOSAGE

Symptoms: The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation.

Treatment: If symptomatic hypotension should occur, supportive treatment should be instituted. Valsartan is not removed from the plasma by hemodialysis.

STORAGE

Store below 30^{o}C

KEEP ALL MEDICATIONS OUT OF REACH OF CHILDREN

PRESENTATION

VALZAAR 40/80/160: It is available as hard gelatin capsule contains in a strip pack of 10 capsules.

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Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Vill. Bhud & Makhnu Majra, Baddi-173 205,
Teh. Nalagarh, Dist. Solan (H.P.), INDIA.