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

VALZAAR-80 MG TABLETS AND VALZAAR-160 MG TABLETS

VALSARTAN TABLETS 80MG, VALSARTAN TABLETS 160 MG

BRAND OR PRODUCT NAME

VALZAAR-80 MG TABLETS

VALZAAR-160 MG TABLETS

NAME AND STRENGTH OF ACTIVE SUBSTANCE(S)

VALZAAR-80 MG TABLETS

Each film coated tablet contains:

Valsartan USP 80 mg

Colours: Titanium dioxide and Red oxide of Iron

VALZAAR-160 MG TABLETS

Each film coated tablet contains:

Valsartan USP 160 mg

Colours: Titanium dioxide and Yellow oxide of Iron

PRODUCT DESCRIPTION

VALZAAR-80 MG TABLETS

Brick red colored, oval shaped, biconvex, film coated tablets with break line on both sides.

VALZAAR-160 MG TABLETS

Yellow colored, oval shaped, biconvex, film coated tablets with break line on both sides.

DOSAGE FORM

Film coated tablet

PHARMACODYNAMICS / PHARMACOKINETICS

Pharmacodynamics

Valsartan is an angiotensin II receptor antagonist. Angiotensin II (Ang II), the principal pressor agent of the renin-angiotensin system is formed from angiotensin I (Ang I) in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). The actions of angiotensin II include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and ventricular hypertrophy, 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.

Another angiotensin II receptor, which is present in many tissues, is the AT2 receptor, but AT2 does not mediate the pressor responses. Valsartan has much greater affinity 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.

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.

Valsartan does not inhibit ACE Which converts Ang I to Ang II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with cough.

Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation

Pharmacokinetics

Valsartan is rapidly absorbed after oral doses, with a bioavailability of about 23 %. Peak plasma concentrations of valsartan occur 2 to 4 hours after an oral dose. It is between 94 and 97 % bound to plasma proteins. Valsartan is not significantly metabolized and is excreted mainly via the bile as unchanged drug. The terminal elimination half-life is about 5 to 9 hours. Following an oral dose about 83 % is excreted in the faeces and 13 % in urine.

Special Populations

Elderly: A somewhat higher systemic exposure to valsartan was observed in some elderly than in young subjects; however, this has not been shown to have any clinical significance.

Impaired Renal Function: As expected for a compound where renal clearance accounts for only 30 % of total plasma clearance, no correlation was seen between renal function and systemic exposure to valsartan. Dose adjustment is therefore not required in patients with renal impairment. No studies have been performed in patients undergoing dialysis. However, valsartan is highly bound to plasma protein and is unlikely to be removed by dialysis.

Hepatic Impairment: About 70% of the absorbed dose is excreted in the bile mainly as unchanged compound. Valsartan does not undergo extensive biotransformation, and as expected, systemic exposure to valsartan is not correlated with the degree of liver dysfunction. No dose adjustment for valsartan is therefore necessary in patients with hepatic insufficiency of nonbiliary origin and without cholestasis. The AUC with valsartan has been observed to approximately double in patients with biliary cirrhosis or biliary obstruction

INDICATION

Treatment of hypertension.

RECOMMENDED DOSAGE AND MODE OF ADMINISTRATION

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. The antihypertensive effect is substantially present within 2 weeks and maximal effects are seen after 4 weeks. In patients whose blood pressure is not adequately controlled, the daily dose may be increased to 320 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 or without food.

Elderly: No dose adjustment is required in elderly patients.

Renal impairment: No dose adjustment is required for patients with a creatinine clearance >10 ml/min

Hepatic impairment: Valsartan is contraindicated in patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis. In patients with mild to moderate hepatic impairment without cholestasis, the dose of valsartan should not exceed 80 mg.

Paediatric patients

Hypertension

Children and adolescents 6 to 18 years of age

The initial dose is 40 mg once daily for children weighing below 35 kg and 80 mg once daily for those weighing 35 kg or more. The dose should be adjusted based on blood pressure response

Weight	Maximum dose
18 kg to <35 kg	80 mg
35 kg to <80 kg	160 mg
80 kg to 160 kg	320 mg

It is not recommended to use in paediatric patients with renal and hepatic impairment.

It is not recommended for patients <6 years old.

CONTRAINDICATIONS

-Hypersensitivity to the active substance or to any of the excipients.

- Severe hepatic impairment, biliary cirrhosis and cholestasis.

- Second and third trimester of pregnancy

WARNINGS AND PRECAUTIONS

Hyperkalaemia

Concomitant use with potassium supplements, salt substitutes containing potassium, or other agents that may increase potassium levels (heparin, etc.) is not recommended. Monitoring of potassium should be undertaken as appropriate.

Impaired renal function

There is currently no experience on the safe use in patients with a creatinine clearance <10 ml/min and patients undergoing dialysis, therefore valsartan should be used with caution in these patients. No dose adjustment is required for adult patients with creatinine clearance >10 ml/min

Hepatic impairment

In patients with mild to moderate hepatic impairment without cholestasis, valsartan should be used with caution

Sodium- and/or volume-depleted patients

Sodium and/or volume depletion should be corrected before starting treatment with valsartan.

Renal artery stenosis

In patients with bilateral renal artery stenosis or stenosis to a solitary kidney, the safe use of valsartan has not been established.

Short-term administration of valsartan to twelve patients with renovascular hypertension secondary to unilateral renal artery stenosis did not induce any significant changes in renal haemodynamics, serum creatinine, or blood urea nitrogen (BUN). However, other agents that affect the renin-angiotensin system may increase blood urea and serum creatinine in patients with unilateral renal artery stenosis, therefore monitoring of renal function is recommended when patients are treated with valsartan.

Kidney transplantation

There is currently no experience on the safe use of valsartan in patients who have recently undergone kidney transplantation.

Primary hyperaldosteronism

Patients with primary hyperaldosteronism should not be treated with valsartan as their renin-angiotensin system is not activated.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

As with all other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy (HOCM).

Pregnancy

Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.

In patients whose renal function may depend on the activity of the renin-angiotensin system, treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotaemia and in rare cases with acute renal failure and/or death. As valsartan is an angiotensin II antagonist, it cannot be excluded that the use of valsartan may be associated with impairment of the renal function.

INTERACTIONS WITH OTHER MEDICAMENTS

No clinically significant pharmacokinetic interactions have been reported with the concurrent administration of valsartan with atenolol, digoxin, cimetidine, furosemide, glyburide, or indomethacin, 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

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 angiotensin receptor blockers, concomitant use of potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors. Due to the lack of experience with concomitant use of valsartan and lithium, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

NSAIDs

Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid>3 g/day), and non-selective NSAIDs and angiotensin II antagonists are administered simultaneously, attenuation of the antihypertensive effect may occur with increased risk of worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.

STATEMENT ON USAGE DURING PREGNANCY AND LACTATION

Pregnancy

As for any drug that also acts directly on the renin-angiotensin-aldosterone system, valsartan should not be used during pregnancy. If pregnancy is detected during therapy, valsartan should be discontinued as soon as possible.

Valsartan therapy exposure during the second and third trimesters is known to induce human fetotoxicity and potential risk of birth defects. There have been reports of spontaneous abortion, oligohydroaminos and newborn renal dysfunction, when pregnant women have inadvertently taken valsartan.

Lactating woman

It is not known whether valsartan is excreted in human milk. Valsartan was excreted in the milk of lactating rats. Because no information is available regarding the use of valsartan during breastfeeding, valsartan is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

ADVERSE EFFECTS / UNDESIRABLE EFFECTS

Reports from controlled clinical studies in patients with hypertension, the overall incidence of adverse reactions (ADRs) was comparable with placebo and is consistent with the pharmacology of valsartan. The incidence of ADRs did not appear to be related to dose or treatment duration and also showed no association with gender, age or race.

The ADRs reported from clinical studies, post-marketing experience and laboratory findings are listed below.

Hypertension

Blood and lymphatic system disorders

Decrease in haemoglobin, Decrease in haematocrit, Neutropenia, Thrombocytopenia

Immune system disorders

Hypersensitivity including serum sickness

Metabolism and nutrition disorders

Increase of serum potassium

Ear and labyrinth system disorders

Vertigo

Vascular disorders

Vasculitis

Respiratory, thoracic and mediastinal disorders

Cough

Gastrointestinal disorders

Abdominal pain

Hepato-biliary Disorders

Elevation of liver function values including increase of serum bilirubin.

Skin and subcutaneous tissue disorders

Angioedema, Rash, Pruritus

Musculoskeletal and connective tissue disorders

Myalgia

Renal and urinary disorders

Renal failure and impairment, Elevation of serum creatinine

General disorders and administration site conditions

Fatigue

OVERDOSE AND TREATMENT

Symptoms

Overdose with valsartan may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock.

Treatment

The therapeutic measures depend on the time of ingestion and the type and severity of the symptoms; stabilization of the circulatory condition is of prime importance. If hypotension occurs, the patient should be placed in a supine position and blood volume correction should be undertaken. If the ingestion is recent, vomiting should be induced. The usual treatment would be i.v. infusion of normal saline solution. Valsartan is not removed from the plasma by haemodialysis.

STORAGE CONDITIONS

Store below 30^{o}C. Protect from moisture.

PACKAGING AVAILABLE

Valsartan tablets are packed in Blister pack using Cold Forming Blister foil sealed with Aluminum foil with heat seal lacquer coating. Blister strip contains 14 tablets. Such blister strips containing 14 tablets are packed into boxes of 14's and 28's along with product information leaflet. Not all presentations may be available locally.

DATE OF REVISION OF PACKAGE INSERT

27th February, 2013

torrent

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA.