PRODUCT NAME	:	Valzaar H	**COUNTRY :** Malaysia		**LOCATION :** Indrad		**Supersedes A/W No.:**
ITEM / PACK	:	Insert	**NO. OF COLORS:** 1		**REMARK :**		
DESIGN STYLE	:	Front / Back	**PANTONE SHADE NOS.:**		**SUBSTRATE :**		
CODE	:	xxxxxxxx-5253	**Activities**	**Department**	**Name**	**Signature**	**Date**
DIMENSIONS (MM)	:	180 x 390	Prepared By	**Pkg.Dev**			
ART WORK SIZE	:	S/S	Reviewed By	**Pkg.Dev**			
DATE	:	26-04-2024	Approved By	**Quality**			

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

VALZAAR H TABLETS
(160 MG + 12.5 MG)

(Valsartan and Hydrochlorothiazide Tablets USP 160 mg + 12.5 mg)

BRAND OR PRODUCT NAME

VALZAAR H TABLETS (160 MG + 12.5 MG)

NAME AND STRENGTH OF ACTIVE SUBSTANCE(S)

Valsartan and Hydrochlorothiazide Tablets USP 160 mg +12.5 mg

Each film coated tablet contains:

Valsartan USP	160 mg
Hydrochlorothiazide USP	12.5 mg

PRODUCT DESCRIPTION

VALZAAR H TABLETS (160 MG + 12.5 MG):

Pink colored, oval shaped, beveled edge, biconvex, film coated tablets debossed with "1072" on one side and plain on other side.

DOSAGE FORM

Film coated Tablets

PHARMACODYNAMICS / PHARMACOKINETICS

Pharmacodynamics

The active hormone of the Renin-Angiotensin-Aldosterone System (RAAS) is angiotensin II, which is formed from angiotensin I through ACE. Angiotensin II binds to specific receptors located in the cell membranes of various tissues. It has a wide variety of physiological effects, including in particular both direct and indirect involvement in the regulation of blood pressure. As a potent vasoconstrictor, angiotensin II exerts a direct pressor response. In addition, it promotes sodium retention and stimulation of aldosterone secretion.

Valsartan is an orally active and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following ATI receptor blockade with valsartan may stimulate the unblocked AT2 receptor, which appears to counterbalance the effect of the AT1 receptor. Valsartan does not exhibit any partial agonist activity at the AT1 receptor and has much greater affinity for the AT1 receptor than for the AT2 receptor.

Valsartan does not inhibit ACE, also known as kininase II, which converts Ang I to Ang II and degrades bradykinin. No potentiation of bradykinin-related side effects should be expected.

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

Administration of valsartan to patients with hypertension results in reduction of blood pressure without affecting pulse rate.

Onset of antihypertensive activity occurs within 2 hours, and the peak reduction of blood pressure is achieved within 4 to 6 hours. The antihypertensive effect persists over 24 hours after dosing. During repeated dosing, the maximum reduction in blood pressure with any dose is generally attained within 2 to 4 weeks and is sustained during long term therapy. Combined with hydrochlorothiazide, a significant additional reduction in blood pressure is achieved.

The site of action of thiazide diuretics is primarily in the renal distal convoluted tubule. It has been reported that there is a high affinity receptor in the renal cortex with the primary binding site for the thiazide diuretic action and inhibition of NaCl transport in the distal convoluted tubule. The mode of action of thiazides is through inhibition of the Na+Cl- symporter perhaps by competing for the Cl--site affecting mechanisms of electrolyte reabsorption: - directly increasing excretion of sodium and chloride in approximate equivalent amounts, -Indirectly, diuretic action reducing 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 co-administration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of sec matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use 50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI:1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for sec. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1. 7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (-25,000 mg) and OR 7. 7 (5. 7-10.5) for the highest cumulative dose (-100,000 mg).

Pharmacokinetics

Valsartan

Absorption of valsartan after oral administration is rapid, although the amount absorbed varies widely. Mean absolute bioavailability for valsartan is 23%. Valsartan reported multi exponential decay kinetics (t1/2 alpha < 1 hour and t1/2 beta about 9 hours).

The pharmacokinetics of valsartan are linear in the dose range tested. There is no change in the kinetics of valsartan on repeated administration, and little accumulation when dosed once daily. Plasma concentrations were reported to be similar in males and females.

Valsartan is highly bound to serum protein (94 to 97%), mainly serum albumin. Steady-state volume of distribution is low (about 17 L). Plasma clearance is relatively slow (about 2 L/h) when compared with hepatic blood flow (about 30 L/h). Of the absorbed dose of valsartan, 70% is excreted in the faeces and 30% in the urine, mainly as unchanged compound.

With food, the area under the plasma concentration curve (AUC) of valsartan is reduced, although from about 8 hours post dosing plasma valsartan concentrations are similar for the fed and fasted group. This reduction in AUC, however, is not accompanied by a clinically significant reduction in the therapeutic effect.

Elderly

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

Renal Impairment

No dose adjustment is required for patients with a creatinine clearance of 30 to 70 ml/min.

In patients with severe renal impairment (Creatinine clearance <30 mL/min) and patients undergoing dialysis, no data are available for use of this fixed dose combination. Valsartan is highly bound to plasma protein, and is not to be removed by dialysis, whereas clearance of hydrochlorothiazide will be achieved by dialysis. Renal clearance of hydrochlorothiazide is composed of passive filtration and active secretion into the renal tubule. As expected for a compound which is cleared almost exclusively via the kidneys, renal function has a marked effect on the kinetics of hydrochlorothiazide (see section CONTRAINDICATION)

Hepatic impairment

In patients with mild to moderate hepatic dysfunction, exposure to Valsartan was increased approximately twofold compared with healthy volunteers. There is no data available on the use of valsartan in patients with severe hepatic dysfunction.

Hepatic disease does not significantly affect the pharmacokinetics of hydrochlorothiazide, and no dose reduction is considered necessary.

Hydrochlorothiazide

The absorption of hydrochlorothiazide after an oral dose is rapid (tmax about 2 hours). The distribution and elimination kinetics have generally been described by a bi-exponential decay function, with a terminal half-life of 6 to 15 hours.

The increase in mean AUC is linear and dose proportional in the therapeutic range. There is no change in the kinetics of hydrochlorothiazide on repeated dosing, and accumulation is minimal when dosed once daily.

Absolute bioavailibility of hydrochlorothiazide is 60 to 80% after oral administration, with> 95% of the absorbed dose being excreted as unchanged compound in the urine, and about 4% as the hydrolysate, 2-amino-4-chloro-m-benzenedisulfonamide.

Concomitant administration with food has been reported to both increase and decrease the systemic availability of hydrochlorothiazide compared with the fasted state. The magnitude of these effects is small and has little clinical importance.

Valsartan/hydrochlorothiazide

The systemic availability of hydrochlorothiazide is reduced by about 30% when co administered with valsartan. The kinetics of valsartan is not markedly affected by the co-administration of hydrochlorothiazide. This reported interaction has no impact on the combined use of valsartan and hydrochlorothiazide, since a clear antihypertensive effect, greater than that obtained with drug given alone, or placebo has been reported.

Special Populations

Elderly

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INDICATION

Treatment of hypertension.

Indicated for the treatment of hypertension in patients whose blood pressure is not adequately controlled by monotherapy. These fixed dose combinations should be used as second-line therapy.

DOSAGE AND ADMINISTRATION

The recommended dose is 1 tablet per day. When clinically appropriate 160 mg valsartan and 12.5 mg hydrochlorothiazide may be used.

Valzaar H should be administered consistently with or without food. No dosage adjustment is required for patients with mild to moderate renal impairment (creatinine clearance > 30 mL/min). In patients with mild to moderate hepatic impairment without cholestasis the daily dose of valsartan should not exceed 80mg. Patients with severe renal or hepatic impairment, biliary cirrhosis or cholestasis must not take Valzaar H.

The safety and efficacy of Valzaar H have not established in children.

CONTRAINDICATIONS

- Hypersensitivity to valsartan, hydrochlorothiazide, other sulfonamide or to any of the excipient of fixed dose combination of valsartan and hydrochlorothiazide
- Pregnancy
- Severe hepatic impairment, biliary Cirrhosis and cholestasis.
- Anuria, severe renal impairment (creatinine clearance <30 mL/mm)
- Refractory hypokalemia, hyponatremia, hypercalcemia, and symptomatic hyperuricemia.

WARNINGS AND PRECAUTIONS

Hydrochlorothiazide

Acute Respiratory Toxicity

Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, VALZAAR H TABLETS should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Serum electrolyte changes

Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other drugs that may increase potassium levels (heparin, etc.) should be used with caution. Thiazide diuretics can precipitate new onset hypokalemia or exacerbate pre-existing hypokalemia. Thiazide diuretics should be administered with caution in patients with conditions involving enhanced potassium loss, for example salt losing nephropathies and prerenal (cardiogenic) impairment of kidney function. If hypokalemia is accompanied by clinical signs (e.g. muscular weakness, paresis, or ECG alterations), Valzaar H should be discontinued. Correction of hypokalemia and any coexisting hypomagnesemia is recommended prior to the initiation of thiazides. Potassium and magnesium serum concentrations should be checked periodically. All patients receiving thiazide diuretics should be monitored for imbalances in electrolytes, particularly potassium. Thiazide diuretics can precipitate new onset hyponatremia and hypochloremia alkalosis or exacerbate pre-existing hyponatremia. Hyponatremia, accompanied by neurological symptoms (nausea, progressive disorientation, apathy) has been observed in isolated cases. Regular monitoring of serum sodium concentrations is recommended.

Patients with sodium- and/or volume-depletion

In severely sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur in rare cases after initiation of therapy with Valzaar H. Valzaar H should be used only after correction of any pre-existing sodium and/or volume depletion otherwise 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 i.v infusion of normal saline. Treatment can be continued once the blood pressure has stabilized.

Patients with renal artery stenosis

Valzaar H should be used with caution to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis to a solitary kidney, since blood urea and serum creatinine may increase in such patients.

Renal impairment

Renal function has a marked effect on the kinetics of hydrochlorothiazide (see section PHARMACOKINETICS - Renal Impairment). Valzaar H should be used with caution in patients with moderate renal impairment (creatinine clearance > 30 mL/min). Periodic checks of serum potassium, creatinine and uric acid levels are advisable. Patients with severe renal impairment (creatinine clearance < 30mL/min) should not take Valzaar H (see section - CONTRAINDICATION).

Hepatic impairment

In patients with mild to moderate hepatic impairment without cholestasis, Valzaar H should be used with caution (see section PHARMACOKINETICS - Hepatic Impairment). Patients with severe hepatic impairment, biliary cirrhosis or cholestasis should not take Valzaar H (see section CONTRAINDICATION).

Angioedema

Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue has been reported in patients treated with valsartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Valzaar H should be immediately discontinued in patients who develop angioedema, and Valzaar H should not be re-administered.

Systemic lupus erythematosus

Thiazide diuretics, including hydrochlorothiazide, have been reported to exacerbate or activate systemic lupus erythematosus.

Other metabolic disturbances

Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol and triglycerides. Like other diuretics, hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricemia and precipitate gout in susceptible patients. Thiazides decrease urinary calcium excretion and may cause mild elevation of serum calcium in the absence of known disorders of calcium metabolism. Since hydrochlorothiazide can increase serum calcium concentrations, it should be used with caution in patients with hypercalcemia. Marked hypercalcemia unresponsive to thiazide withdrawal or ≥12 mg/dL may be evidence of an underlying thiazide independent hypercalcemic process. Pathological changes in the parathyroid gland of patients with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. If hypercalcemia occurs, further diagnostic clarification is necessary.

General

Hypersensitivity reactions to hydrochlorothiazide are more likely in patients with allergy and asthma.

Acute Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, has been associated with an idiosyncratic reaction resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to week of a drug initiation. Untreated acute-angle closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatment may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle closure glaucoma may include a history of sulfonamide or penicillin allergy. Patients with heart failure/post-myocardial infarction 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 or angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia, and in rare cases with acute renal failure and/or death. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function.

Renin-Angiotensin System

Dual Blockade of the Renin-Angiotensin System (RAS) : Caution is required while co-administering ARBs, including valsartan, with other agents blocking the RAS such as ACEIs or aliskiren (see section INTERACTIONS, subsection dual blockade of the RAS).

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)J with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC.

INTERACTIONS WITH OTHER MEDICAMENTS

Valsartan-hydrochlorothiazide

The following drug interactions may occur due to both components (valsartan and/or hydrochlorothiazide) of Valzaar H:

Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors, angiotensin II receptor antagonists or thiazides. Since renal clearance of lithium is reduced by thiazides, the risk of lithium toxicity may presumably be increased further with Valzaar H. Therefore, careful monitoring of serum lithium concentrations is recommended during concomitant use.

Valsartan

The following potential drug interactions may occur due to the valsartan component of Valzaar H:

Dual blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs, or aliskiren: The concomitant use of ARBs, including valsartan, with other agents acting on the RAS is associated with an increased incidence of hypotension, hyperkalemia, and changes in renal function compared to monotherapy. It is recommended to monitor blood pressure, renal function and electrolytes in patients on Valzaar H and other agents that affect the RAS (see section WARNINGS AND PRECAUTIONS).

The concomitant use of ARBs - including valsartan - or of ACEIs with aliskiren, should be avoided in patients with severe renal impairment (GFR < 30 mL/min) (see section WARNINGS AND PRECAUTIONS).

The concomitant use of ARBs - including valsartan- or of ACEIs with aliskiren is contraindicated in patients with Type 2 diabetes (see section CONTRAINDICATIONS).

Potassium: Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other drugs that may alter potassium levels (heparin, etc.) should be used with caution and with frequent monitoring of potassium.

Non-Steroidal Anti-Inflammatory Agents (NSAIDs) including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur.

Furthermore, in patients who are elderly, volume-depleted (including those on diuretic therapy), or have compromised renal function, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function. Therefore, monitoring of renal function is recommended when initiating or modifying the treatment in patients on valsartan who are taking NSAIDs concomitantly.

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 (e.g. rifampin, cyclosporine) or efflux transporter (e.g. ritonavir) may increase the systemic exposure to valsartan.

In monotherapy with valsartan, no drug interactions of clinical significance have been found with the following drugs: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide.

Hydrochlorothiazide

The following potential drug interactions may occur due to the thiazide component of Valzaar H:

Other anti-hypertensive drugs: Thiazides potentiate the antihypertensive action of other antihypertensive drugs (e.g. guanethidine, methyldopa, beta blockers, vasodilators, calcium channel blockers, ACE inhibitors, Angiotensin Receptor Blockers (ARBs) and Direct Renin Inhibitors (DRIs)).

Skeletal muscle relaxants: Thiazides, including hydrochlorothiazide, potentiate the action of skeletal muscle relaxants such as curare derivatives.

Medicinal products affecting serum potassium level: The hypokalemic effect of diuretics may be increased by concomitant administration of kaliuretic diuretics, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G, salicylic acid derivatives or antiarrhythmics (see section WARNINGS AND PRECAUTIONS).

Medicinal products affecting serum sodium level: The hyponatremic effect of diuretics may be intensified by concomitant administration of drugs such as antidepressants, antipsychotics, antiepileptics, etc. Caution is advised in long-term administration of these drugs (see section WARNINGS AND PRECAUTIONS).

Antidiabetic agents: Thiazides may alter glucose tolerance. It may be necessary to adjust the dosage of insulin and of oral antidiabetic agents.

Digitalis glycosides: Thiazide-induced hypokalemia or hypomagnesemia may occur as unwanted effects, favoring the onset of digitalis-induced cardiac arrhythmias. (see section WARNINGS AND PRECAUTIONS).

NSAIDs and Cox-2 selective inhibitors: Concomitant administration of NSAIDs (e.g. salicylic acid derivative, indomethacin) may weaken the diuretic and antihypertensive activity of the thiazide component of Valzaar H. Concurrent hypovolemia may induce acute renal failure.

Allopurinol: Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol.

Amantadine: Co-administration of thiazide diuretics (including hydrochlorothiazide) may increase the risk of adverse effects caused by amantadine

Antineoplastic agents (e.g. cyclophosphamide, methotrexate): Concomitant use of thiazide diuretics may reduce the renal excretion of cytotoxic agents and enhance their myelosuppressive effects.

Anticholinergic agents: The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate. Conversely prokinetic drugs such as cisapride may decrease the bioavailability of thiazide-type diuretics.

Ion exchange resins: Absorption of thiazide diuretics, including hydrochlorothiazide, is decreased by cholestyramine or colestipol. However, staggering the dosage of hydrochlorothiazide and resin such that hydrochlorothiazide is administered at least 4 h before or 4-6 h after the administration of resins would potentially minimize the interaction..

Vitamin D: Administration of thiazide diuretics, including hydrochlorothiazide, with vitamin D or with calcium salts may potentiate the rise in serum calcium.

Ciclosporin: Concomitant treatment with ciclosporine may increase the risk of hyperuricemia and gout-type complications.

Calcium salts: Concomitant use of thiazide type diuretics may lead to hypercalcemia by increasing tubular calcium reabsorption.

Diazoxide: Thiazide diuretics may enhance the hyperglycaemic effect of diazoxide.

Methyldopa: There have been reports in the literature of hemolytic anemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

Alcohol, barbiturates or narcotics: Concomitant administration of thiazide diuretics with alcohol, barbiturates, or narcotics may potentiate orthostatic hypotension.

Pressor amines: Hydrochlorothiazide may reduce the response to pressor amines such as noradrenaline. The clinical significance of this effect is uncertain and not sufficient to preclude their use.

PREGNANCY AND LACTATION

Women of child-bearing potential

As for any drug that also acts directly on the RAAS, Valzaar H should not be used in women planning to become pregnant. Healthcare professionals prescribing any agents acting on the RAAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy.

Pregnancy

As for any drug that also acts directly on the RAAS, Valzaar H should not be used during pregnancy (see section CONTRAINDICATIONS). Due to the mechanism of action of angiotensin II antagonists, a risk for the foetus cannot be excluded. In utero exposure to angiotensin converting enzyme (ACE) inhibitors (a specific class of drugs acting on the renin-angiotensin-aldosterone system RAAS) given to pregnant women during the second and third trimesters has been reported to cause injury and death to the developing foetus. In addition, in retrospective data, first trimester use of ACE inhibitors has been associated with a potential risk of birth defects. There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction, when pregnant women have inadvertently taken valsartan. Intrauterine exposure to thiazide diuretics, including hydrochlorothiazide, is associated with fetal or neonatal jaundice or thrombocytopenia, and may be associated with other adverse reactions that have occurred in adults. If pregnancy is detected during therapy, Valzaar H should be discontinued as soon as possible.

Breast-feeding

It is not known whether valsartan is excreted in human milk. Valsartan was excreted in the milk of lactating rats. Hydrochlorothiazide crosses the placenta and is excreted in human milk. Thus, it is not advisable to use Valzaar H in breast-feeding mothers.

Fertility

There is no information on the effects of valsartan or hydrochlorothiazide on human fertility. Studies in rats did not show any effects of valsartan or hydrochlorothiazide on fertility.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

As with other antihypertensive agents, it is advisable to exercise caution when driving or operating machinery.

ADVERSE EFFECTS / UNDESIRABLE EFFECTS

Respiratory, thoracic and mediastinal disorders

Frequency 'very rare': Acute respiratory distress syndrome (ARDS)

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.

Table 1. Frequency of adverse reactions with valsartan/hydrochlorothiazide

Metabolism and nutrition disorders	
Uncommon	Dehydration
Nervous system disorders	
Uncommon	Paraesthesia
Very rare	Dizziness
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 oedema
Gastrointestinal disorders	
Very rare	Diarrhoea
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, Hypokalaemia, Hyponatraemia, Elevation of Blood Urea Nitrogen, Neutropenia

Table 2. Frequency of adverse reactions with valsartan

Blood and lymphatic system disorders	
Not known	Decrease in haemoglobin, decrease in haematocrit, thrombocytopenia
Immune system disorders	
Not known	Other hypersensitivity/allergic reactions including serum sickness
Metabolism and nutrition disorders	
Not known	Increase of serum potassium, hyponatraemia
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

Table 3. Frequency of adverse reactions with hydrochlorothiazide

Hydrochlorothiazide has been extensively prescribed for many years, frequently in higher doses than those administered with Valzaar H. The following adverse reactions have been reported in patients treated with monotherapy of thiazide diuretics, including hydrochlorothiazide:

Blood and lymphatic system disorders	
Rare	Thrombocytopenia sometimes with purpura
Very rare	Agranulocytosis, leucopenia, haemolytic anaemia, bone marrow failure
Not known	Aplastic anemia
Immune system disorders	
Very rare	Hypersensitivity reactions
Metabolism and nutrition disorders	
Very common	Hypokalaemia, blood lipids increased (mainly at higher doses)
Common	Hyponatraemia, hypomagnesaemia, hyperuricaemia
Rare	Hypercalcaemia, hyperglycaemia, glycosuria and worsening of diabetic metabolic state
Very rare	Hypochloraemic alkalosis
Psychiatric disorders	
Rare	Depression, sleep disturbances
Nervous system disorders	
Rare	Headache, dizziness, paraesthesia
Eye disorders	
Frequency 'not known'	Choroidal effusion, acute myopia, acute angle-closure glaucoma
Cardiac disorders	
Rare	Cardiac arrhythmias
Vascular disorders	
Common	Postural hypotension
Respiratory, thoracic and mediastinal disorders	
Very rare	Respiratory distress including pneumonitis and pulmonary oedema
Gastrointestinal disorders	
Common	Loss of appetite, mild nausea and vomiting
Rare	Constipation, gastrointestinal discomfort, diarrhoea
Very rare	Pancreatitis
Hepatobiliary disorders	
Rare	Intrahepatic cholestasis or jaundice
Renal and urinary disorders	
Not known	Renal dysfunction, acute renal failure
Skin and subcutaneous tissue disorders	
Common	Urticaria and other forms of rash
Rare	Photosensitisation
Very rare	Necrotising vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus
Not known	Erythema multiforme
General disorders and administration site conditions	
Not known	Pyrexia, asthenia
Musculoskeletal and connective tissue disorders	
Not known	Muscle spasm
Reproductive system and breast disorders	
Common	Impotence
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Frequency 'not known':	Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)

Description of selected adverse reactions

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed.

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. In addition, the following signs and symptoms may occur due to an overdose of the hydrochlorothiazide component: nausea, somnolence, hypovolaemia, and electrolyte disturbances associated with cardiac arrhythmias and muscle spasms.

Treatment

The therapeutic measures depend on the time of ingestion and the type and severity of the symptoms, stabilisation of the circulatory condition being of prime importance.

If hypotension occurs, the patient should be placed in the supine position and salt and volume supplementation should be given rapidly.

Valsartan cannot be eliminated by means of haemodialysis because of its strong plasma binding behaviour whereas clearance of hydrochlorothiazide will be achieved by dialysis.

This medicine should be kept out of the reach and sight of children.

STORAGE CONDITIONS

Do not store above 30°C. Protect from moisture.

PACKAGING AVAILABLE

VALZAAR H TABLETS 160 MG + 12.5 MG are packed in Alu-Alu blister of 14 Tablets. Such blister containing 14 tablets are packed in boxes of 28's and 98's along with the package insert. Not all presentations may be available locally.

DATE OF REVISION OF PACKAGE INSERT

1 May, 2024

Torrent PHARMA

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