For the use only of a Registered Medical Practitioner

PRESCRIBING INFORMATION

STARVAL HCT

(Valsartan and Hydrochlorothiazide Tablets 80+12.5mg/160+25mg)

COMPOSITION

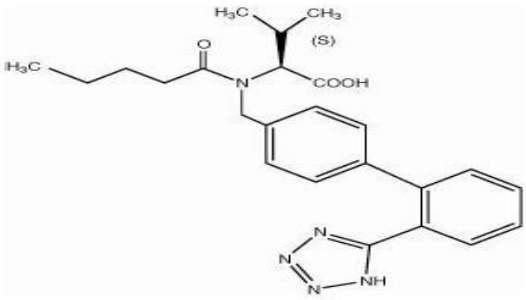
STARVAL HCT
(Valsartan and Hydrochlorothiazide Tablets 80+12.5mg)
Each film coated tablet contains:
Valsartan USP 80 mg
Hydrochlorothiazide Ph Eur… 12.5 mg

STARVAL HCT
(Valsartan and Hydrochlorothiazide Tablets 160+25mg)
Each film coated tablet contains:
Valsartan USP 160 mg
Hydrochlorothiazide Ph Eur… 25 mg

DESCRIPTION

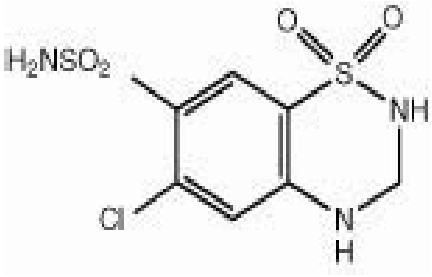
STARVAL HCT (valsartan and hydrochlorothiazide) is a combination of valsartan, an orally active, specific angiotensin II receptor blocker (ARB) acting on the AT_1 receptor subtype, and hydrochlorothiazide, a diuretic.

Valsartan, a nonpeptide molecule, is chemically described 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

Hydrochlorothiazide is a thiazide diuretic chemically described as 6-chloro-3, 4-dihydro-2H-1, 2, 4-benzothiadiazine-7-sulphonamide 1, 1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$, its molecular weight is 297.7, and its structural formula is



Hydrochlorothiazide

PRODUCT DESCRIPTION

For 80 + 12.5 mg Strength : White to off white, film coated, oval shaped tablets debossed with **'VH 1'** on one side and plain on the other side.

For 160 + 25 mg Strength: White to off white, film coated, oval shaped tablets debossed with **'VH 3'** on one side and plain on the other side.

PHARMACOLGY

- **Pharmacodynamics**

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 AT_1 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 AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT_1 receptor than for the AT_2 receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT_1 receptor about one 200^{th} 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.

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.

On administration of multiple-doses 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. On administration of multiple-doses in hypertensive patients, valsartan had no notable effects on total cholesterol, fasting triglycerides, fasting serum glucose, or uric acid.

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces 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 coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics. The mechanism of the antihypertensive effect of thiazides is unknown. After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

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 SCC 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 SCC. 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 clear 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/hydrochlorothiazide
The systemic availability of hydrochlorothiazide is reduced by about 30% when co-administered with valsartan. The kinetics of valsartan are not markedly affected by the co-administration of hydrochlorothiazide. This observed interaction has no impact on the combined use of valsartan and hydrochlorothiazide.

Valsartan
Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23%. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%, although from about 8 hours post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

The steady-state volume of distribution of valsartan after intravenous administration is about 17 litres, indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94 – 97%), mainly serum albumin. Valsartan is not biotransformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive. Valsartan shows multiexponential decay kinetics ($t_{½\alpha}$ <1 hour and $t_{½ß}$ about 9 hours). Valsartan is primarily eliminated in faeces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 l/hours and its renal clearance is 0.62 l/hours (about 30% of total clearance). The half-life of valsartan is 6 hours.

Hydrochlorothiazide
The absorption of hydrochlorothiazide, after an oral dose, is rapid (t_{max} about 2 hours), with similar absorption characteristics for both suspension and tablet formulations. Absolute bioavailability of hydrochlorothiazide is 60–80% after oral administration. 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 minimal clinical importance. 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.

The distribution and elimination kinetics have generally been described by bi-exponential decay function. The apparent volume of distribution is 4–8 L/kg. Circulating hydrochlorothiazide is bound to serum proteins (40–70%), mainly serum albumin. Hydrochlorothiazide also accumulates in erythrocytes at approximately 1.8 times the level in plasma. For hydrochlorothiazide,> 95% of the absorbed dose being excreted as unchanged compound in the urine. The renal clearance is composed of passive filtration and active secretion into the renal tubule. The terminal half-life is 6 – 15 hours.

Special populations

Elderly
A somewhat higher systemic exposure to valsartan was observed in some elderly subjects than in young subjects; however, this has not been shown to have any clinical significance. Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.

Renal impairment
At the recommended dose of the fixed dose combination of valsartan and hydrochlorothiazide no dose adjustment is required for patients with a creatinine clearance of 30-70ml/min. In patients with severe renal impairment (creatinine clearance < 30ml/min) and patients undergoing dialysis no data are available for the fixed dose combination of valsartan and hydrochlorothiazide. 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 **CONTRAINDICATIONS**).

Hepatic impairment
In patients with mild to moderate hepatic dysfunction, exposure to valsartan may increase approximately 2-fold. There is no data available on the use of valsartan in patients with severe hepatic dysfunction (see **CONTRAINDICATIONS**). Hepatic disease does not significantly affect the pharmacokinetics of hydrochlorothiazide, and no dose adjustment is considered necessary.

INDICATIONS / USAGE

Treatment of hypertension.

The fixed dose combination of valsartan and hydrochlorothiazide is indicated 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

STARVAL HCT tablets (containing valsartan and hydrochlorothiazide) are available in two strengths of 80/12.5mg and 160/25mg. They are not able to deliver all approved dose regimens of the fixed dose combination of valsartan and hydrochlorothiazide; other approved dosage forms and strengths of fixed dose combination of valsartan and hydrochlorothiazide should be used in such cases. The general dosage recommendations of the fixed dose combination of valsartan and hydrochlorothiazide are presented below:

The recommended dose of the fixed dose combination of valsartan and hydrochlorothiazide is one tablet per day. When clinically appropriate either 80mg valsartan and 12.5mg hydrochlorothiazide or 160mg valsartan and 12.5 mg hydrochlorothiazide or 320 mg valsartan and 12.5 mg hydrochlorothiazide may be used. When necessary 160 mg valsartan and 25 mg hydrochlorothiazide or 320 mg valsartan and 25 mg hydrochlorothiazide may be used. The maximum antihypertensive effect is seen within 2 to 4 weeks.

No dosage adjustment is required for patients with mild to moderate renal impairment (creatinine clearance> 30 ml/min). No dosage adjustment is required in patients with mild to moderate hepatic insufficiency of non-biliary origin and without cholestasis. The safety and efficacy of the fixed dose combination of valsartan and hydrochlorothiazide has not been established in children.

CONTRAINDICATIONS

- Hypersensitivity to valsartan, hydrochlorothiazide, other sulfonamide-derived medicinal products or to any of the excipients.
- Pregnancy (see **USE IN SPECIAL POPULATIONS**).
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
- Severe renal impairment (creatinine clearance < 30 ml/min), anuria.
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia, and symptomatic hyperuricaemia.
- Concomitant use of angiotensin receptor antagonists (ARBs) - including valsartan- or of angiotensin-converting enzyme inhibitors (ACEIs) with aliskiren in patients with Type 2 diabetes

WARNINGS AND PRECAUTIONS

Serum electrolyte changes

Valsartan
Concomitant use with potassium supplements, potassium-sparing diuretics, 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.

Hydrochlorothiazide
Hypokalaemia has been reported under treatment with thiazide diuretics, including hydrochlorothiazide. Frequent monitoring of serum potassium is recommended.

Treatment with thiazide diuretics, including hydrochlorothiazide has been associated with hyponatraemia and hypochloraemic alkalosis. Thiazides, including hydrochlorothiazide increase the urinary excretion of magnesium, which may result in hypomagnesaemia. Calcium excretion is decreased by thiazide diuretics. This may result in hypercalcaemia.

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Sodium, and/or volume-depleted patients

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 **STARVAL HCT**. **STARVAL HCT** 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.

Renal artery stenosis

STARVAL HCT 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.

Patients with renal impairment

Renal function has a marked effect on the kinetics of hydrochlorothiazide. **STARVAL HCT** 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 **STARVAL HCT.**

Patients with hepatic impairment

In patients with mild to moderate hepatic impairment without cholestasis, **STARVAL HCT** should be used with caution. Patients with severe hepatic impairment, biliary cirrhosis or cholestasis should not take **STARVAL HCT.**

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. **STARVAL HCT** should be immediately discontinued in patients who develop angioedema, and **STARVAL HCT** 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.

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] 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.

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 weeks 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.

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)

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, **STARVAL HCT** should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

- **Effects on ability to drive and use machines**

No studies on the effects on the ability to drive and use machines have been performed. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

DRUG INTERACTIONS

Interactions related to both valsartan and hydrochlorothiazide

The following drug interactions may occur due to both components (valsartan and/or hydrochlorothiazide) of **STARVAL HCT**:

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors and thiazide, including hydrochlorothiazide. 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.

Interactions related to valsartan

The following potential drug interactions may occur due to the valsartan component of **STARVAL HCT**:

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 Co-Diovan 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, ciclosporin) 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.

Interactions related to hydrochlorothiazide

The following potential drug interactions may occur due to the thiazide component of **STARVAL HCT**:

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 levels
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 levels
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 Co-Diovan. 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 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 ciclosporin 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.

ADVERSE REACTIONS / SIDE EFFECTS

Adverse reactions reported more frequently with valsartan plus hydrochlorothiazide are presented below according to system organ class. Adverse reactions known to occur with each component given individually but which have not been reported with Valsartan/hydrochlorothiazide may occur during treatment with valsartan/ hydrochlorothiazide.

Table: Frequency of adverse reactions with valsartan/hydrochlorothiazide	
Blood and lymphatic system disorders	
Not known	Neutropenia
Very rare	Arthralgia
Metabolism and nutrition disorders	
Uncommon	Dehydration
Not known	Hypokalaemia, hyponatraemia
Nervous system disorders	
Very rare	Dizziness
Uncommon	Paraesthesia
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
Renal and urinary disorders	
Not known	Renal impairment
General disorders and administration site conditions	
Uncommon	Fatigue
Investigations	
Not known	Blood uric acid increased, blood bilirubin and blood creatinine increased, blood urea increased

Additional information on the individual components
Adverse reactions previously reported with one of the individual components may be potential undesirable effects with the fixed dose combination of valsartan and hydrochlorothiazide as well.

Table: 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	Blood potassium increased
Ear and labyrinth disorders	
Uncommon	Vertigo
Vascular disorders	
Not known	Vasculitis
Gastrointestinal disorders	
Uncommon	Abdominal pain
Hepatobiliary disorders	
Not known	Liver function test abnormal
Skin and subcutaneous tissue disorders	
Not known	Angioedema, rash, dermatitis bullous, pruritus
Renal and urinary disorders	
Not known	Renal failure

Hydrochlorothiazide has been extensively prescribed for many years, frequently in higher doses than those administered with the fixed dose combination of valsartan and hydrochlorothiazide. The following adverse reactions have been reported with monotherapy of thiazide diuretics, including hydrochlorothiazide:

Table: Frequency of adverse reactions with hydrochlorothiazide	
Blood and lymphatic system disorders	
Rare	Thrombocytopenia sometimes with purpura
Very rare	Agranulocytosis, leucopenia, haemolytic anaemia,

	bone marrow depression
Not known	Aplastic anaemia
Immune system disorders	
Very rare	Vasculitis necrotizing, hypersensitivity reactions - respiratory distress including pneumonitis and pulmonary oedema
Metabolism and nutrition disorders	
Very common	Mainly at higher doses blood lipids increased
Common	Hypomagnesaemia, hyperuricaemia, decreased appetite
Rare	Hypercalcaemia, hyperglycaemia, glycosuria and worsening of diabetic metabolic state
Very rare	Alkalosis hypochloraemic
Eye disorders	
Rare	Visual impairment particularly in the first few weeks of treatment
Not known	Choroidal effusion, acute myopia, acute angle-closure glaucoma
Psychiatric disorders	
Rare	Sleep disorders
Nervous system disorders	
Rare	Headache, dizziness, depression and paresthesia
Cardiac disorders	
Rare	Cardiac arrhythmias
Vascular disorders	
Common	Orthostatic hypotension, which may be aggravated by alcohol, anesthetics or sedatives
Respiratory, thoracic and mediastinal disorders	
Very rare	Acute respiratory distress syndrome (ARDS)
Gastrointestinal disorders	
Common	Mild nausea and vomiting
Rare	Abdominal discomfort, constipation and diarrhoea
Very rare	Pancreatitis
Hepatobiliary disorders	
Rare	Intrahepatic cholestasis or jaundice
Skin and subcutaneous tissue disorders	
Common	Urticaria and other forms of rash
Rare	Photosensitisation
Very rare	Toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus
Not known	Erythema multiforme
Musculoskeletal and connective tissue disorders	
Not known	Muscle spasms
Renal and urinary disorders	

Not known	Acute renal failure, renal disorder
Reproductive system and breast disorders	
Common	Erectile dysfunction
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Not known	Non-melanoma skin cancer (Basal cell circanoma and Squamous cell carcinoma) ***Description of selected adverse reactions*** *Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulativen dose-dependant association between HCTZ and NMSC has been observed.*

Other reported adverse effects:

Valsartan
General: flushing
Gastrointestinal: dry mouth, increased appetite
Infections and infestations: bronchitis, bronchitis acute, influenza, gastroentritis, sinusitis, upper respiratory tract infections and urinary tract infections, viral infections
Musculoskeletal: back pain, muscle cramps, pain in extremity
Nervous system: somnolence
Psychiatric: anxiety
Renal and Urinary: pollakiuria
Respiratory, thoracic, and mediastinal: dyspnea, nasal congestion, sinus congestion, pharyngeal pain, pharyngitis, bronchospasm, epistaxsis
Genitourinary: decreased libido, dysuria
Skin and subcutaneous tissue: Hyperhydrosis
Metabolic: gout

Hydrochlorothiazide
Body as a whole: weakness, fever
Digestive: sialadenitis
Metabolic: hyperglycaemia, glycosuria,
Musculoskeletal: muscle spasm
Nervous system: nervousness
Renal: interstitial nephritis
Special senses: xanthopsia
Vascular: orthostatic hypotension which may be aggravated by alcohol, anaesthetics or sedatives
Genitourinary: erectile dysfunction

Valsartan and hydrochlorothiazide

Clinical laboratory tests: hyperkallemia
Respiratory: chest pain
Musculoskeletal: rhabdomyolysis

Nervous system: hypoesthesia
Ear and labyrinth disorders: Otitis media
Musculoskeletal: ligament sprain
Special senses: vision disturbance

USE IN SPECIAL POPULATIONS

- **Pregnancy**

As for any drug that acts directly on the RAAS, **STARVAL HCT** must not be used during pregnancy (see section CONTRAINDICATIONS). Due to the mechanism of action of angiotensin II antagonists, a risk for the fetus cannot be excluded. ACE inhibitors (a specific class of drugs acting on the renin angiotensin aldosterone system- RAAS) given during the second and third trimesters has been reported to cause injury and death to the developing fetus. In addition, first trimester use of ACE inhibitors has been reported with a potential risk of birth defects. Thiazide diuretics, including hydrochlorothiazide during intrauterine exposure, is reported to be associated with foetal or neonatal thrombocytopenia, and may be associated with other adverse reactions that have occurred in adults.

Spontaneous abortion, oligohyramnios and newborn renal dysfunction has been reported when pregnant women have inadvertently taken valsartan. As for any drug that also acts directly on the RAAS, valsartan and hydrochlorothiazide should not be used during pregnancy or women planning to become pregnant. Healthcare professionals prescribing any agents acting on the RAAS should counsel women on childbearing potential about potential risk of these agents during pregnancy. If pregnancy is detected during therapy, **STARVAL HCT** should be discontinued as soon as possible.

- **Lactation**

It is not known whether valsartan is transferred into human milk. Valsartan was transferred into the milk of lactating rats. Hydrochlorothiazide crosses the placenta and is transferred into human milk. Thus, it is not advisable to use **STARVAL HCT** in breast-feeding mothers.

- **Fertility**

There is no information on the effects of valsartan or hydrochlorothiazide on human fertility.

- **Pediatrics**

The fixed dose combination of valsartan and hydrochlorothiazide is not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.

- **Geriatrics**

A somewhat higher systemic exposure to valsartan was observed in some elderly subjects than in young subjects; however, this has not been shown to have any clinical significance. Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.

- **Renal Impairment**

No dose adjustment is required for patients with mild to moderate renal impairment (creatinine clearance ≥30ml/min). Due to the hydrochlorothiazide component, fixed dose combination of valsartan and hydrochlorothiazide is contraindicated in patients with severe renal impairment (see **CONTRAINDICATION, WARNINGS AND PRECAUTIONS and PHARMACOLOGY; Pharmacokinetics**).

- **Hepatic Impairment**

(see **CONTRAINDICATION; WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

OVERDOSAGE

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.

STORAGE: Store at a temperature below 30 ºC, protected from moisture.

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN

SUPPLY: Blister pack of 10's, Box of 3 x 10's

Date of Revision: April 2025

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