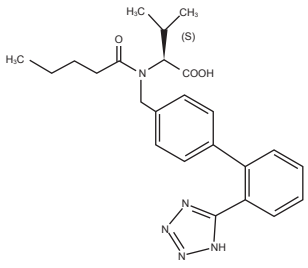
Cova-H™

[Valsartan+Hydrochlorothiazide]

کووا-ایچ

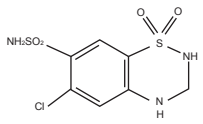
Tablets 80mg + 12.5mg & 160mg + 12.5mg

DESCRIPTION
Cova-H (Valsartan + Hydrochlorothiazide) is a fixed dose combination of Valsartan and Hydrochlorothiazide. Valsartan is a non-peptide molecule, an orally active and specific angiotensin II receptor blocker (ARB) acting on the AT_1 receptor subtype. Its chemical name is N-(1-oxopentyl)-N-[[2'-(1H-tetrazol-5-yl) [1, 1'-biphenyl]-4-yl] methyl]-L-Valine. Its molecular formula is $C_{24}H_{29}N_5O_3$ and structural formula is:



Valsartan

Hydrochlorothiazide is a thiazide diuretic. Its chemical name is 6-chloro-3, 4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its molecular formula is $C_7H_8ClN_3O_4S_2$ and structural formula is:



Hydrochlorothiazide

QUALITATIVE AND QUANTITIVE COMPOSITION
Cova-H (Valsartan + Hydrochlorothiazide) is available for oral combination as:

Cova-H Tablets 80mg + 12.5mg
Each film-coated tablet contains:
Valsartan USP...80mg
Hydrochlorothiazide USP...12.5mg

Cova-H Tablets 160mg + 12.5mg
Each film-coated tablet contains:
Valsartan USP...160mg
Hydrochlorothiazide USP...12.5mg

CLINICAL PHARMACOLOGY
Mechanism of Action
Valsartan
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.

Hydrochlorothiazide
Hydrochlorothiazide affects 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 mechanism of the antihypertensive effect of thiazides is unknown.

Pharmacokinetics
Valsartan
Absorption
Following oral administration of Valsartan alone peak plasma concentrations of Valsartan are reached in 2 to 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%. However this reduction in AUC is not accompanied by a clinically significant reduction in the therapeutic affect and Valsartan can therefore be given with or without food.

Distribution
Valsartan is highly bound to serum proteins (94-97%), mainly serum albumin.

Metabolism
Valsartan is not metabolized 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.

Excretion
Valsartan is primarily eliminated in feces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. The half-life of Valsartan is 6 hours.

Hydrochlorothiazide
Absorption
The absorption of Hydrochlorothiazide, after an oral dose, is rapid (t_{max} about 2h). The increase in mean AUC is linear and dose proportional in the therapeutic range. The effect of food on Hydrochlorothiazide absorption, if any, has little clinical significance. Absolute bioavailability of Hydrochlorothiazide is 70% after oral administration.

Distribution
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 3 times the level in plasma.

Excretion
About 70% of an orally administered dose of Hydrochlorothiazide is eliminated in the urine as unchanged drug.

Special Population
Elderly
Exposure (measured by AUC) to Valsartan is higher by 70% and the half-life is longer by 35% in the elderly than in the young. Systemic clearance of Hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.

Renal Impairment
There is no apparent correlation between renal function (measured by creatinine clearance) and exposure (measured by AUC) to Valsartan in patients with different degrees of renal impairment. In the presence of renal impairment, mean peak plasma levels and AUC values of Hydrochlorothiazide are increased and the urinary excretion rate is reduced. In patients with mild to moderate renal impairment, a 3-fold increase in Hydrochlorothiazide AUC has been observed. In patients with severe renal impairment an 8-fold increase in AUC has been observed.

Hepatic Impairment
About 70% of the absorbed Valsartan dose is excreted in the bile, mainly as unchanged compound. The AUC with Valsartan has been observed to approximately double in patients with mild or moderate hepatic impairment including patients with biliary obstructive disorders. Hepatic disease does not significantly affect the pharmacokinetics of Hydrochlorothiazide.

THERAPEUTIC INDICATIONS
Cova-H (Valsartan + Hydrochlorothiazide) is indicated for the treatment of hypertension to lower blood pressure:
- In patients not adequately controlled with monotherapy.
- As initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals.

Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.

DOSAGE & ADMINISTRATION
The recommended dose of Cova-H (Valsartan + Hydrochlorothiazide) 80mg + 12.5mg is one tablet once daily. Dose titration with the individual components is recommended. In each case, up-titration of individual components to the next dose should be followed in order to reduce the risk of hypotension and other adverse events.

When clinically appropriate direct change from monotherapy to the fixed combination may be considered in patients whose blood pressure is not adequately controlled on Valsartan or Hydrochlorothiazide monotherapy, provided the recommended dose titration sequence for the individual components is followed.

The clinical response to Cova-H (Valsartan + Hydrochlorothiazide) should be evaluated after initiating therapy and if blood pressure remains uncontrolled, the dose may be increased by increasing either one of the components to a maximum dose of Cova-H (Valsartan + Hydrochlorothiazide) 320mg + 25mg.

The antihypertensive effect is substantially present within 2 weeks.

In most patients, maximal effects are observed within 4 weeks. However, in some patients, 4-8 weeks treatment may be required. This should be taken into account during dose titration.

Special Population
Elderly
No dose adjustment is required in elderly patients.

Renal or Hepatic Impairment
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.

Pediatric Patients
Cova-H (Valsartan + Hydrochlorothiazide) is not recommended for use in children below the age of 18 years due to lack of data on safety and efficacy.

ADVERSE REACTIONS
Following adverse reaction have been reported during treatment with Valsartan and Hydrochlorothiazide combination:

Uncommon
Dehydration, parasthesia, vision blurred, tinnitus, hypotension, cough, myalgia and fatigue.

Very Rare
Dizziness, diarrhea and arthralgia.

Not known
Syncope, non cardiogenic pulmonary oedema, impaired renal function, serum uric acid increased, serum bilirubin and serum creatinine increased, hypokalemia, hyponatremia, elevation of blood urea nitrogen and neutropenia.

CONTRAINDICATIONS
The combination of Valsartan and Hydrochlorothiazide is contraindicated;
- In patients with known hypersensitivity to Valsartan or Hydrochlorothiazide or to any excipient of the product.
- In patients with hypersensitivity to other sulfonamide-derived drugs.
- In severe hepatic impairment, biliary cirrhosis and cholestasis.
- In severe renal impairment (creatinine clearance < 30 ml/min), anuria.
- In refractory hypokalemia, hyponatremia, hypercalcemia and symptomatic hyperuricemia.
- In concomitant use with aliskiren containing products in patients with diabetes mellitus.

Pregnancy
The combination of Valsartan and Hydrochlorothiazide is contraindicated in second and third trimester of pregnancy and should not be initiated during pregnancy. Unless continued 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 should be stopped immediately, and, if appropriate, alternative therapy should be started.

Nursing Mothers
No information is available regarding the use of Valsartan during breastfeeding. Hydrochlorothiazide is excreted in human milk. Therefore the use of Valsartan and Hydrochlorothiazide combination during breastfeeding is not recommended. A decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

PRECAUTIONS
- 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 the combination of Valsartan and Hydrochlorothiazide , or the treatment should start under close medical supervision.
- In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure and in patients with primary hyperaldosteronism) the combination of Valsartan and Hydrochlorothiazide should not be administered.
- The combination of Valsartan and Hydrochlorothiazide should not be used to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, since blood urea and serum creatinine may increase in such patients.
- The combination of Valsartan and Hydrochlorothiazide should be immediately discontinued in patients who develop angioedema and should not be re-administered.
- As with all other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy.
- In patients with mild to moderate hepatic impairment without cholestasis, combination of Valsartan and Hydrochlorothiazide should be used with caution.
- Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.
- Hydrochlorothiazide can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. 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 treatments may need to be considered if the intraocular pressure remains uncontrolled.
- When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.
- Photosensitivity reactions have been reported with thiazide diuretics. If photoseneitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration is necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.
- Hypersensitivity reactions may occur with Hydrochlorothiazide in patients with allergy and asthma.
- Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides.
- Hydrochlorothiazide may cause or exacerbate hyperuricemia and precipitate gout in susceptible patients.
- Dual blockade of the RAAS through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended. If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.
- Hydrochlorothiazide decreases urinary calcium excretion and may cause elevations of serum calcium. Monitor calcium levels in patients with hypercalcemia.

DRUG INTERACTIONS
Lithium
Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists or thiazides. Monitor lithium levels in patients taking the combination.

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.

Transporters
Valsartan is a substrate of the hepatic uptake transporter OATP1B1/OATP1B3 and the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (eg. rifampin, ciclosporin) or efflux transporter (eg. ritonavir) may increase the systemic exposure to Valsartan.

Antidiabetic agents
Thiazide diuretics, including Hydrochlorothiazide, may increase blood glucose. It may prove necessary to readjust 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.

Medicinal products affecting serum sodium level
The hyponatraemic effect of diuretics may be intensified by concomitant administration of drugs such as antidepressants, antipsychotics, antiepileptics, etc.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
Concomitant administration of NSAIDs (e.g. salicylic acid derivatives indomethacin) including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors) may weaken the diuretic and antihypertensive activity of the thiazide component.

Allopurinol
Coadministration of thiazide diuretics (including Hydrochlorothiazide) may increase the incidence of hypersensitivity reactions to allopurinol.

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.

Pressor amines
The effect of pressor amines (e.g. noradrenaline) may be decreased.

Cholestyramine and colestipol resins
Single doses of cholestyramine or colestipol resins reduced the absorption of Hydrochlorothiazide by up to 85% and 43% respectively. Staggering the dosage of Hydrochlorothiazide and ion exchange resins such that Hydrochlorothiazide is administered atleast 4 hours after the administration of resins would potentially minimize the interaction.

Corticosteroids, ACTH
Electrolyte depletion, particularly hypokalemia, may be increased with concomitant treatment with thiazide.

Probenacid & Sulfinpyrazone
Thiazide diuretics, may increase serum uric acid levels, and the dose of uricosuric agents such as probenacid or sulfinpyrazone may need to be increased.

Hypokalemic agents
The hypokalemic effect of diuretics may be increased by concomitant administration of kaliuretic diuretics, amphotericin, carbenoxolone, penicillin G, salicylic acid derivatives or antiarrhythmics.

Cyclosporine
Concomitant treatment of thiazide with cyclosporine may increase the risk of hyperuricemia and gout-type complications.

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

Tetracyclines
Concomitant administration of tetracyclines and thiazide diuretics increases the risk for tetracycline induced increase in urea. This interaction is probably not applicable to doxycycline.

Alcohol, anaesthetics and sedatives
Potentiation of orthostatic hypotension may occur with concomitant administration with thiazide.

Iodine contrast media
In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of the iodine product. Patients should be rehydrated before the administration.

Amantadine & cytotoxic drugs
Co-administration of thiazide diuretics, including Hydrochlorothiazide, may increase the risk of adverse effects caused by amantadine, and may reduce the renal excretion of cytotoxic drugs (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

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

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

Carbamazepine
Patients receiving Hydrochlorothiazide concomitantly with carbamazepine may develop hyponatremia. Such patients should therefore be advised about the possibility of hyponatremic reactions and should be monitored accordingly.

Other anti-hypertensive agents
The combination of Valsartan and Hydrochlorothiazide may increase the effects of other agents with antihypertensive properties (e.g. guanethidine, methyldopa, vasodilators, ACEI, ARBs, beta-blockers, calcium channel blockers and DRIs).

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: dizziness, nausea, somnolence, hypovolemia, hypotension 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. If the ingestion is recent, a sufficient amount of activated charcoal should be administered. Otherwise the usual treatment would be intravenous infusion of normal saline solution. Valsartan cannot be eliminated by means of hemodialysis because it is strongly bound to plasma proteins whereas clearance of Hydrochlorothiazide will be achieved by dialysis.

STORAGE
Store at 25°C (Excursions permitted between 15°C-30°C).
Protect from sunlight and moisture.
The expiry date refers to the product corrcetly stored at the required conditions.

HOW SUPPLIED
Cova-H (Valsartan + Hydrochlorothiazide) Tablets 80mg + 12.5mg are available in pack of 14's.
Cova-H (Valsartan + Hydrochlorothiazide) Tablets 160mg + 12.5mg are available in pack of 14's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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